Copy for the Elected Office (EO/US)

PCT/BE00/00026

09/937007

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

LECHIEN, Monique
UCB, S.A. - Intellectual Property Department
Allée de la Recherche 60
B-1070 Brussels
BELGIQUE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
24 September 2001 (24.09.01)

Applicant's or agent's file reference
16.76.WO

IMPORTANT NOTIFICATION

International application No.
PCT/BE00/00026

International filing date (day/month/year)
23 March 2000 (23.03.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
SCANNEL, Ralph
6 Cider Mill Road
Hopkinson, MA 01748
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
SCANNELL, Ralph
6 Cider Mill Road
Hopkinson, MA 01748
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
Correction of typographical error.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Ki-Nam HA
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 December 2000 (12.12.00)	
International application No. PCT/BE00/00026	**Applicant's or agent's file reference** 16.76.WO
International filing date (day/month/year) 23 March 2000 (23.03.00)	**Priority date** (day/month/year) 26 March 1999 (26.03.99)
Applicant SCANNEL, Ralph et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 September 2000 (29.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

09/937667

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/BG 00/ 00026	12/10/2000	18/10/1999
Applicant		
POPOV, Ivaylo Nicolaev		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BG 00/00026

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 H04L29/06 G06F1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 H04L G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 500 897 A (HARTMAN JR ROBERT C) 19 March 1996 (1996-03-19)	1,4
A	column 2, line 63 -column 3, line 12	5,6
A	EP 0 869 651 A (ERICSSON TELEFON AB L M) 7 October 1998 (1998-10-07) claims 1,2	1-21
A	WO 99 34551 A (BARKAN MORDHAI) 8 July 1999 (1999-07-08) claim 1	1-21
A	US 5 812 764 A (HEINZ SR MICHAEL WILLIAM) 22 September 1998 (1998-09-22) column 2, line 55 -column 3, line 22; claims 1,3	1-21

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2001	13/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Veen, G

PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/BG 00/00026

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 06928 A (SPRING TECHNOLOGIES INC) 11 February 1999 (1999-02-11) page 16, left-hand column, line 15 -page 17, left-hand column, line 8	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BG 00/00026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5500897 A	19-03-1996	US 5444780 A	22-08-1995
		DE 69425793 D	12-10-2000
		DE 69425793 T	12-04-2001
		EP 0635790 A	25-01-1995
		JP 2628619 B	09-07-1997
		JP 7036559 A	07-02-1995
EP 0869651 A	07-10-1998	WO 9844693 A	08-10-1998
		AU 6632598 A	22-10-1998
		NO 994221 A	30-09-1999
		US 6199165 B	06-03-2001
WO 9934551 A	08-07-1999	AU 4119399 A	19-07-1999
US 5812764 A	22-09-1998	NONE	
WO 9906928 A	11-02-1999	US 6119096 A	12-09-2000
		AU 730215 B	01-03-2001
		AU 7123198 A	22-02-1999
		AU 8763398 A	22-02-1999
		BR 9815555 A	17-07-2001
		EP 1029298 A	23-08-2000
		WO 9906901 A	11-02-1999

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
16.76.WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/BE 00/ 00026	23/03/2000	26/03/1999
Applicant		
UCB, S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the dat of mailing of this int rnational search report, submit comments to this Authority.

6. The figure of th **drawings** to b publish d with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] Non of th figur s.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DE 00/00026

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/08 C07D295/12 C07D295/14 C07D307/14 C07D307/52
A61K31/495 C07D401/04 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 616 596 A (BASHA ANWER ET AL) 1 April 1997 (1997-04-01) claims ---	1
A	US 4 525 358 A (BALTES EUGENE ET AL) 25 June 1985 (1985-06-25) cited in the application claims ---	1
A	US 4 282 233 A (VILANI FRANK J) 4 August 1981 (1981-08-04) cited in the application claims ---	1
A	US 5 066 658 A (DEMERS, JAMES P. ET AL) 19 November 1991 (1991-11-19) example 75 --- -/--	21-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2000	02/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pauwels, G

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 00/00026

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 438 062 A (GANGULY ASHIT K ET AL) 1 August 1995 (1995-08-01) example 11	23,24

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/RE 00/00026

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
US 5616596	A	01-04-1997	US	5288751	A	22-02-1994
			AT	178049	T	15-04-1999
			AU	673040	B	24-10-1996
			AU	5666094	A	08-06-1994
			CA	2136077	A	26-05-1994
			DE	69324152	D	29-04-1999
			DE	69324152	T	28-10-1999
			EP	0667855	A	23-08-1995
			ES	2131185	T	16-07-1999
			GR	3030354	T	30-09-1999
			JP	8503200	T	09-04-1996
			WO	9411342	A	26-05-1994
US 4525358	A	25-06-1985	AT	8140	T	15-07-1984
			AU	544066	B	16-05-1985
			AU	8023182	A	12-08-1982
			BA	97198	B	02-08-1999
			BA	97199	B	02-08-1999
			CA	1199918	A	28-01-1986
			CY	1307	A	06-12-1985
			DE	3260282	D	02-08-1984
			DK	5388	A,B,	07-01-1988
			DK	44082	A,B,	07-08-1982
			EP	0058146	A	18-08-1982
			ES	509358	D	01-08-1983
			ES	8307776	A	01-11-1983
			ES	521548	D	01-08-1984
			ES	8406455	A	01-11-1984
			FI	820318	A,B,	07-08-1982
			GR	75407	A	13-07-1984
			HK	86485	A	15-11-1985
			JP	1463099	C	28-10-1988
			JP	57149282	A	14-09-1982
			JP	63011353	B	14-03-1988
			LT	2553	R	28-02-1994
			LV	5494	A	10-03-1994
			MY	27987	A	31-12-1987
			NO	820297	A,B,	09-08-1982
			NZ	199650	A	06-07-1984
			PL	234935	A	09-05-1983
			PL	239687	A	18-07-1983
			PT	74390	A,B	01-03-1982
			SU	1227113	A	23-04-1986
			SU	1310397	A	15-05-1987
			SU	1287749	A	30-01-1987
			YU	23782	A	30-06-1985
			YU	223584	A	30-06-1985
			ZA	8200752	A	29-12-1982
			HU	184989	B	28-11-1984
US 4282233	A	04-08-1981	AT	9695	T	15-10-1984
			AU	543054	B	28-03-1985
			AU	7186281	A	24-12-1981
			CA	1160230	A	10-01-1984
			CY	1405	A	22-04-1988
			DE	3166441	D	08-11-1984
			DK	263481	A	20-12-1981
			EP	0042544	A	30-12-1981

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/RE 00/00026

Patent document cited in search report	Publication date	Patent family member(s)		Publication dat
US 4282233 A		ES	503085 D	01-11-1982
		ES	8300779 A	01-02-1983
		FI	811878 A,B,	20-12-1981
		HK	94387 A	18-12-1987
		HU	186774 B	30-09-1985
		IE	51303 B	26-11-1986
		IL	63122 A	30-06-1985
		JP	1506964 C	13-07-1989
		JP	57035586 A	26-02-1982
		JP	63055513 B	02-11-1988
		KE	3758 A	02-10-1987
		KR	8500744 B	24-05-1985
		LU	88359 A	04-05-1994
		MY	76187 A	31-12-1987
		NZ	197435 A	30-03-1984
		PH	19252 A	17-02-1986
		PT	73200 A,B	01-07-1981
		SG	70587 G	19-02-1988
		US	4355036 A	19-10-1982
		US	4560688 A	24-12-1985
		US	4831042 A	16-05-1989
		ZA	8104062 A	28-07-1982
US 5066658 A	19-11-1991	NONE		
US 5438062 A	01-08-1995	US	5089496 A	18-02-1992
		US	4826853 A	02-05-1989
		US	5665726 A	09-09-1997
		EP	0685476 A	06-12-1995
		AT	114650 T	15-12-1994
		AU	643946 B	02-12-1993
		AU	5642090 A	29-11-1990
		CA	2053903 A,C	02-11-1990
		CZ	9104144 A	12-05-1993
		DE	69014393 D	12-01-1995
		DE	69014393 T	01-06-1995
		DK	396083 T	06-02-1995
		EP	0396083 A	07-11-1990
		EP	0471750 A	26-02-1992
		ES	2064520 T	01-02-1995
		FI	102609 B	15-01-1999
		IE	66392 B	27-12-1995
		IL	94258 A	07-10-1994
		JP	2863629 B	03-03-1999
		JP	4504724 T	20-08-1992
		KR	9509859 B	29-08-1995
		NO	179674 B	19-08-1996
		NZ	233495 A	25-11-1992
		OA	9521 A	15-11-1992
		WO	9013548 A	15-11-1990
		US	5151423 A	29-09-1992
		ZA	9003303 A	30-01-1991
		AT	116310 T	15-01-1995
		AU	635400 B	18-03-1993
		AU	7285991 A	30-05-1991
		AU	604285 B	13-12-1990
		AU	8336287 A	25-05-1988
		CA	1305147 A	14-07-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BE 00/00026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5438062 A		CA 1321589 A	24-08-1993
		CS 9104143 A	16-09-1992
		DE 3750929 D	09-02-1995
		DE 3750929 T	01-06-1995
		DK 73193 A	21-06-1993
		DK 354688 A	28-06-1988
		EP 0270818 A	15-06-1988
		EP 0330673 A	06-09-1989
		ES 2068179 T	16-04-1995
		FI 891806 A,B,	17-04-1989
		HK 186396 A	11-10-1996
		IE 65174 B	04-10-1995
		JP 6078316 B	05-10-1994
		JP 2500910 T	29-03-1990
		KR 9302489 B	02-04-1993
		NO 882907 A,B,	29-06-1988
		NZ 222347 A	27-03-1990

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
16.76.WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE00/00026	23/03/2000	26/03/1999
International Patent Classification (IPC) or national classification and IPC C07D295/08		
Applicant UCB, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/10/2000	18.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cortés, J Telephone No. +49 89 2399 8206

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BE00/00026

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-46 as originally filed

Claims, No.:

1-24 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 11-12, 19, 22-24.

because:

☒ the said international application, or the said claims Nos. 22-24 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 11-12, 19, 22 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-10, 13-18, 20-21, 23-24

	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10, 13-18, 20-21, 23-24
Industrial applicability (IA)	Yes:	Claims	1-10, 13-18, 20-21
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Contrary to Rule 6.2(a) PCT claims 11 and 12 make reference to the description and they do not contain a reference to claim 1 (Article 6 PCT).

In claim 19 a substituent is defined by the way a compound containing this substituent is metabolized. This functional definition is unclear, since it would require a person skilled in the art to carry out extensive examinations in order to determine whether a given substituent falls within the scope of the claim or not.

It is noted that compounds in which the bond between M and the generic structure is cleaved after essential parts of the pharmacologically active structure are metabolized, would not be a solution to the problem of the invention (i.e. not have the desired pharmacological activity) and therefore lack an inventive step.

In claim 22 a group of diseases is defined by the need of a subject for administration of the claimed compounds. This functional definition is unclear, since it does not enable a person skilled in the art to determine which real diseases actually fall within the scope of this claim (Article 6 PCT).

Claims 22-24 refer to the treatment of a human or animal body by therapy and are therefore excluded from examination according to Rule 67.1 (iv).

No opinion is given for these claims on the question whether they are industrially applicable, since no unified criteria exist in the PCT Contracting States.

Re It m V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statem nt

Reference is made to the following documents:

D1: US-A-5 616 596 (BASHA ANWER ET AL) 1 April 1997 (1997-04-01)

D2: US-A-4 525 358 (BALTES EUGENE ET AL) 25 June 1985 (1985-06-25) cited in the application

D3: US-A-4 282 233 (VILANI FRANK J) 4 August 1981 (1981-08-04) cited in the application

D4: US-A-5 066 658 (DEMERS, JAMES P. ET AL) 19 November 1991 (1991-11-19)

D5: US-A-5 438 062 (GANGULY ASHIT K ET AL) 1 August 1995 (1995-08-01)

Novelty

Present subject matter differs from D1 in the piperazine, piperidine or 4-methylidenyl piperidine moiety (D1: e.g. line 35, column 2 to line 45, column 4), from D2, D3 and D5 in that the compounds must contain an optionally substituted hydroxyamide (or hydroxyurea) function, i.e. in the proviso that at least one of the substituents W or W' must be $-N(OM)C(O)N(R^8)R^9$, $-N(R^8)C(O)N(OM)R^9$ or $-N(OM)C(O)R^8$ (D2: e.g. lines 15-32, column 1; D3: e.g. lines 25-60, column 1; D5: e.g. line 26, column 1 to line 57, column 2) and from D4 in that the hydroxyamide function is linked with the heterocycle at its nitrogen and not at its carbonyl group; or in other words, in that the hydroxyurea function is separated at least by a bond instead of being fused with the heterocycle (D4: e.g. example 75).

It is noted that if it were not for the above mentioned proviso, compounds disclosed in D2, D3, D4 and D5 would fall within the scope of present claims.

Inventive Step

The problem underlying the present invention was the provision of novel compounds having dual properties, each compound possessing both lipoxygenase inhibition as well as antihistaminergic properties (description: e.g. lines 16-18, page 2). These dual biological activity is achieved by combining two structural features, each of them known to be causal for at least one of both effects.

The compounds of the invention could be useful for the treatment of conditions associated with these functionalities, such as asthma, allergy or inflammatory disorders (description: e.g. lines 20-24, page 2 and line 8, page 1 to line 14, page 2).

D4 can be regarded as closest prior art. This document describes a related compound having both structural components, namely a diphenylmethyl-piperidine and a hydroxyurea function (D4: e.g. example 75). D4 also discloses a lipoxygenase inhibitory activity as well as its possible use for the treatment of the above mentioned diseases.

D4 further contains results of assays proving a lipoxygenase inhibitory, a bronchodilating as well as an anti-inflammatory activity of structurally related compounds disclosed therein. Nonetheless, it is noted that no results for example 75 were disclosed.

The specific way by which the mentioned structural components are linked to each other in example 75 is excluded in present set of claims by the above mentioned proviso.

The only structural difference between present compounds and example 75 of D4 is that the diphenylmethyl-piperidine and the hydroxyurea or structurally related functions are separated from each other at least by a bond, instead of being fused with each other.

Even though a antihistaminergic activity was not reported in D4, it was known, e.g. from the prior art cited in present description (e.g. line 27, page 1 to line 9, page 2) that histamine plays a role in the above mentioned diseases.

The biological activity of each structural component was well known from the prior art. D2, D3 and D5 for instance describe compounds with a diaryl-methyl-piperidine, -methyl-piperazine, -methylidenyl-piperidine or related structures with anti-histaminic, anti-allergic and anti-inflammatory activity. D1 and D4 for instance disclose hydroxyurea- and hydroxyamide substituted aromatic compounds with lipoxygenase inhibitory activity, useful for treating asthma, allergies and inflammations.

Since each structural component together with its respective biological activity as well as a combination of both structures with a combined activity was known from the prior art, it was not surprising that present compounds would have the mentioned biological properties.

Industrial Applicability

The patentability is dependent upon the formulation of the claims. The EPO, for instance, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII
Certain defects in the international application

The description does not mention the closest prior art represented by the above cited documents as required by Rule 5.1(a)(ii) and (iii) PCT.

The background and reasoning for the provisos nor the relevant prior art are mentioned in the description (Rule 5.1(a)(ii) and (iii) PCT).

The expression "hereby incorporated by reference" (e.g. line 31-32, page 2) used in the description is irrelevant and unnecessary (Rule 9 (iv) PCT).

Re Item VIII

Certain observations on the international application

Thew excessive use of provisos in claim 1 renders the scope of the claim unclear (Article 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
16.76.WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE00/00026	23/03/2000	26/03/1999
International Patent Classification (IPC) or national classification and IPC C07D295/08		
Applicant UCB, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/10/2000	18.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cortés, J Telephone No. +49 89 2399 8206

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BE00/00026

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-46 as originally filed

Claims, No.:

1-24 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 11-12, 19, 22-24.

because:

   ☒ the said international application, or the said claims Nos. 22-24 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 11-12, 19, 22 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-10, 13-18, 20-21, 23-24

	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10, 13-18, 20-21, 23-24
Industrial applicability (IA)	Yes:	Claims	1-10, 13-18, 20-21
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Contrary to Rule 6.2(a) PCT claims 11 and 12 make reference to the description and they do not contain a reference to claim 1 (Article 6 PCT).

In claim 19 a substituent is defined by the way a compound containing this substituent is metabolized. This functional definition is unclear, since it would require a person skilled in the art to carry out extensive examinations in order to determine whether a given substituent falls within the scope of the claim or not.

It is noted that compounds in which the bond between M and the generic structure is cleaved after essential parts of the pharmacologically active structure are metabolized, would not be a solution to the problem of the invention (i.e. not have the desired pharmacological activity) and therefore lack an inventive step.

In claim 22 a group of diseases is defined by the need of a subject for administration of the claimed compounds. This functional definition is unclear, since it does not enable a person skilled in the art to determine which real diseases actually fall within the scope of this claim (Article 6 PCT).

Claims 22-24 refer to the treatment of a human or animal body by therapy and are therefore excluded from examination according to Rule 67.1 (iv).

No opinion is given for these claims on the question whether they are industrially applicable, since no unified criteria exist in the PCT Contracting States.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US-A-5 616 596 (BASHA ANWER ET AL) 1 April 1997 (1997-04-01)

D2: US-A-4 525 358 (BALTES EUGENE ET AL) 25 June 1985 (1985-06-25) cited in the application

D3: US-A-4 282 233 (VILANI FRANK J) 4 August 1981 (1981-08-04) cited in the application

D4: US-A-5 066 658 (DEMERS, JAMES P. ET AL) 19 November 1991 (1991-11-19)

D5: US-A-5 438 062 (GANGULY ASHIT K ET AL) 1 August 1995 (1995-08-01)

Novelty

Present subject matter differs from D1 in the piperazine, piperidine or 4-methylidenyl piperidine moiety (D1: e.g. line 35, column 2 to line 45, column 4), from D2, D3 and D5 in that the compounds must contain an optionally substituted hydroxyamide (or hydroxyurea) function, i.e. in the proviso that at least one of the substituents W or W' must be $-N(OM)C(O)N(R^8)R^9$, $-N(R^8)C(O)N(OM)R^9$ or $-N(OM)C(O)R^8$ (D2: e.g. lines 15-32, column 1; D3: e.g. lines 25-60, column 1; D5: e.g. line 26, column 1 to line 57, column 2) and from D4 in that the hydroxyamide function is linked with the heterocycle at its nitrogen and not at its carbonyl group; or in other words, in that the hydroxyurea function is separated at least by a bond instead of being fused with the heterocycle (D4: e.g. example 75).

It is noted that if it were not for the above mentioned proviso, compounds disclosed in D2, D3, D4 and D5 would fall within the scope of present claims.

Inventive Step

The problem underlying the present invention was the provision of novel compounds having dual properties, each compound possessing both lipoxygenase inhibition as well as antihistaminergic properties (description: e.g. lines 16-18, page 2). These dual biological activity is achieved by combining two structural features, each of them known to be causal for at least one of both effects.

The compounds of the invention could be useful for the treatment of conditions associated with these functionalities, such as asthma, allergy or inflammatory disorders (description: e.g. lines 20-24, page 2 and line 8, page 1 to line 14, page 2).

D4 can be regarded as closest prior art. This document describes a related compound having both structural components, namely a diphenylmethyl-piperidine and a hydroxyurea function (D4: e.g. example 75). D4 also discloses a lipoxygenase inhibitory activity as well as its possible use for the treatment of the above mentioned diseases.

D4 further contains results of assays proving a lipoxygenase inhibitory, a bronchodilating as well as an anti-inflammatory activity of structurally related compounds disclosed therein. Nonetheless, it is noted that no results for example 75 were disclosed.

The specific way by which the mentioned structural components are linked to each other in example 75 is excluded in present set of claims by the above mentioned proviso.

The only structural difference between present compounds and example 75 of D4 is that the diphenylmethyl-piperidine and the hydroxyurea or structurally related functions are separated from each other at least by a bond, instead of being fused with each other.

Even though a antihistaminergic activity was not reported in D4, it was known, e.g. from the prior art cited in present description (e.g. line 27, page 1 to line 9, page 2) that histamine plays a role in the above mentioned diseases.

The biological activity of each structural component was well known from the prior art. D2, D3 and D5 for instance describe compounds with a diaryl-methyl-piperidine, -methyl-piperazine, -methylidenyl-piperidine or related structures with anti-histaminic, anti-allergic and anti-inflammatory activity. D1 and D4 for instance disclose hydroxyurea- and hydroxyamide substituted aromatic compounds with lipoxygenase inhibitory activity, useful for treating asthma, allergies and inflammations.

Since each structural component together with its respective biological activity as well as a combination of both structures with a combined activity was known from the prior art, it was not surprising that present compounds would have the mentioned biological properties.

Industrial Applicability

The patentability is dependent upon the formulation of the claims. The EPO, for instance, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII
Certain defects in the international application

The description does not mention the closest prior art represented by the above cited documents as required by Rule 5.1(a)(ii) and (iii) PCT.

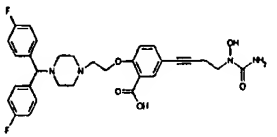
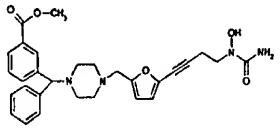
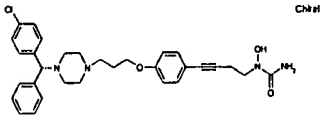
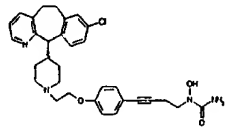
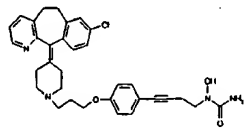
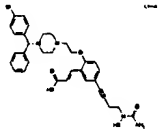
The background and reasoning for the provisos nor the relevant prior art are mentioned in the description (Rule 5.1(a)(ii) and (iii) PCT).

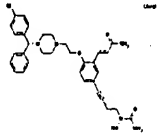
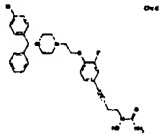
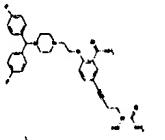
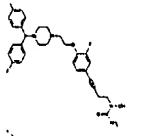
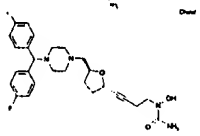
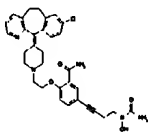
The expression "hereby incorporated by reference" (e.g. line 31-32, page 2) used in the description is irrelevant and unnecessary (Rule 9 (iv) PCT).

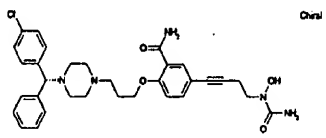
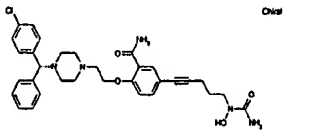
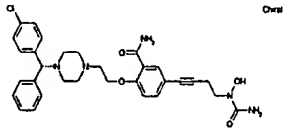
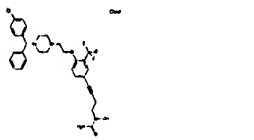
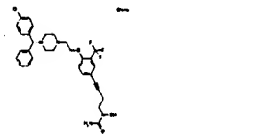
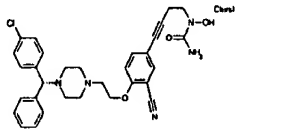
Re Item VIII

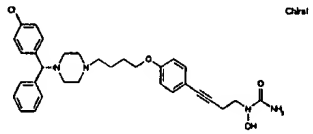
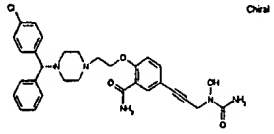
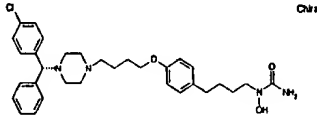
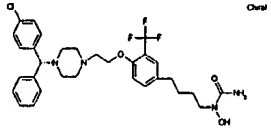
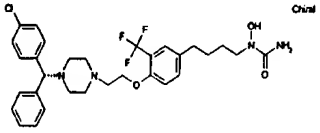
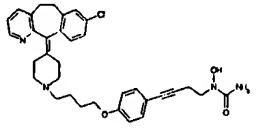
Certain observations on the international application

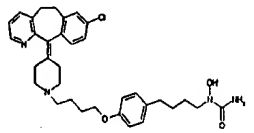
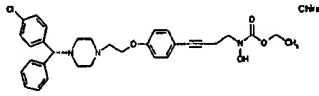
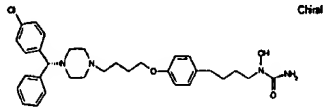
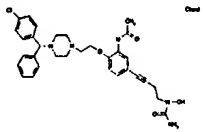
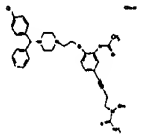
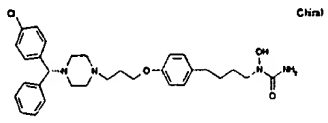
Thew excessive use of provisos in claim 1 renders the scope of the claim unclear (Article 6 PCT).

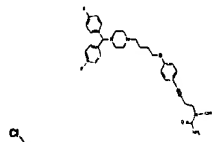
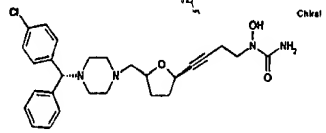
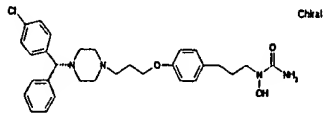
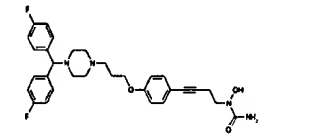
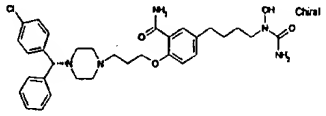
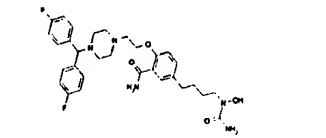
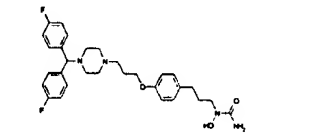
CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
50			2 HCl		579	3,47	5-[4-(aminohydroxycarbonylamino)but-1-ynyl]-2-(2-{4-[bis(4-fluorophenyl)methyl]piperazinyl}ethoxy) benzoic acid
51		RACEMATE			517,1	2,94	methyl 3-{[4-({5-[4-(aminohydroxycarbonylamino)but-1-ynyl](2-furyl)}methyl)piperazinyl]phenylmethyl} benzoate
52		CHIRAL R			547,07	4,54	N-{4-[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl} propoxy)phenyl]but-3-ynyl}amino-N-hydroxyamide
53		RACEMATE			559,1	5,42	amino-N-[4-(4-{2-[4-(8-chloro(5,6,11-trihydrobenzo[b]pyridino[3,2-f][7]annulen-11-yl))piperidyl]ethoxy}phenyl)but-3-ynyl]-N-hydroxyamide
54					571,14	6,44	amino-N-[4-(4-{3-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl]propoxy}phenyl)but-3-ynyl]-N-hydroxyamide
55		CHIRAL R	2 HCl		603,2	4,19	(2E)-3-[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl]prop-2-enoic acid

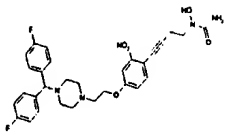
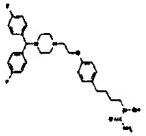
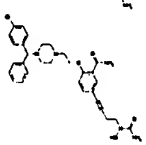
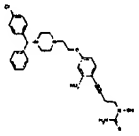
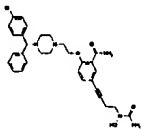
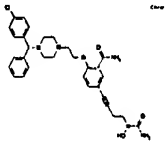
CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
56		CHIRAL R			602	3,44	N-{4-[3-((1E)-2-carbamoylvinyl)-4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]but-3-ynyl}amino-N-hydroxyamide
57		CHIRAL R			551,64	4,35	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}ethoxy)-3-fluorophenyl]but-3-ynyl}amino-N-hydroxyamide
58					578,02	2,71	5-[4-(aminohydroxycarbonylamino)but-1-ynyl]-2-(2-{4-[bis(4-fluorophenyl) methyl]piperazinyl}ethoxy) benzamide
59					552,96	3,92	amino-N-{4-[4-(2-{4-[bis(4-fluorophenyl)methyl]piperazinyl}ethoxy)-3-fluorophenyl]but-3-ynyl}-N-hydroxyamide
60		CHIRAL TRANS			499	2,33	N-{4-[(2S,5S)-5-({4-[bis(4-fluorophenyl) methyl]piperazinyl}methyl)oxolan-2-yl]but-3-ynyl}amino-N-hydroxyamide
61					599,82	5,03	5-[4-(aminohydroxycarbonylamino)but-1-ynyl]-2-{2-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl]ethoxy}benzamide

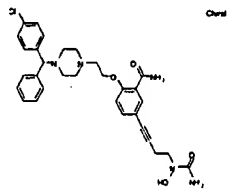
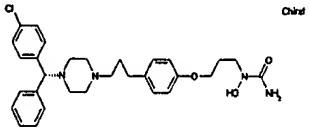
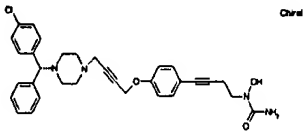
CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
62		CHIRAL R		153 - 155	589,21	3,49	2-{3-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}propoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzamide
63		CHIRAL R			590,06	3,65	2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}ethoxy)-5-[5-(aminohydroxycarbonylamino)pent-1-ynyl]benzamide
64		CHIRAL R	2 HCl	208	576,2	3,14	2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzamide
65		CHIRAL R			5,34	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl]phenylmethyl]piperazinyl}ethoxy)-3-(trifluoromethyl)phenyl]but-3-ynyl}amino-N-hydroxyamide	
66		CHIRAL R	2 HCl		600,36	5,34	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-3-(trifluoromethyl)phenyl]but-3-ynyl}amino-N-hydroxyamide
67		CHIRAL R		557,5	4,1	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl]phenylmethyl]piperazinyl}ethoxy)-3-cyanophenyl]but-3-ynyl}amino-N-hydroxyamide	

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
68		CHIRAL R			560,59	5,05	N-{4-[4-(4-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}butoxy)phenyl]but-3-ynyl}amino-N-hydroxyamide
69		CHIRAL R			561,57	2,63	2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[3-(aminohydroxycarbonylamino)prop-1-ynyl]benzamide
70		CHIRAL R			564,56	5,41	N-{4-[4-(4-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}butoxy)phenyl]butyl}amino-N-hydroxyamide
71		CHIRAL R			604,56	5,84	N-{4-[4-(2-{4-[(1S)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-3-(trifluoromethyl)phenyl]butyl}amino-N-hydroxyamide
72		CHIRAL R	2 HCl		604,44	5,84	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-3-(trifluoromethyl)phenyl]butyl}amino-N-hydroxyamide
73						6,95	amino-N-[4-(4-{4-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl]butoxy}phenyl)but-3-ynyl]-N-hydroxyamide

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
74						7,31	amino-N-[4-{4-{4-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl]butoxy}phenyl)butyl]-N-hydroxyamide
75		CHIRAL R			561,57	5,4	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]but-3-ynyl}ethoxy-N-hydroxycarboxamide
76		CHIRAL R	2 HCl	121- 123	564,64	5,41	N-{4-[4-(4-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}butoxy)phenyl]butyl}amino-N-hydroxyamide
77		CHIRAL R		90 - 95	589,45	3,19	N-[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl]acetamide
78		CHIRAL R	2 HCl	400	589,7	3,19	N-[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl]acetamide
79		CHIRAL R		60 - 65	550,49	4,9	N-{4-[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}propoxy)phenyl]butyl}amino-N-hydroxyamide

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
80				64 - 68	562,5	4,63	amino-N-{4-[4-(4-{4-[bis(4-fluorophenyl)methyl]piperazinyl}butoxy)phenyl]but-3-ynyl}-N-hydroxyamide
81		CHIRAL (R,R,R)		42	496,57	4,39	N-{4-[(2R)-5-({4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}methyl)oxolan-2-yl]but-3-ynyl}amino-N-hydroxyamide
82		CHIRAL R		52 - 90	536,52	2,75	N-{3-[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}propoxy)phenyl]propyl}amino-N-hydroxyamide
83				78	549,1	4,12	amino-N-{4-[4-(3-{4-[bis(4-fluorophenyl)methyl]piperazinyl}propoxy)phenyl]but-3-ynyl}-N-hydroxyamide
84		CHIRAL R		123 - 125	594,3	4	2-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}propoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzamide
85				138 -140	582,5	3,22	5-{4-[(aminocarbonyl)(hydroxy)amino]butyl}-2-(2-{4-[bis(4-fluorophenyl)methyl]-1-piperazinyl}ethoxy)benzamide
86				30 - 80	539,4	3,97	N-{3-[4-(3-{4-[bis(4-fluorophenyl)methyl]-1-piperazinyl}propoxy)phenyl]propyl}-N-hydroxyurea

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
87				65 - 70	580,1	3,74	N-{4-[4-(2-{4-[bis(4-fluorophenyl)methyl]-1-piperazinyl}ethoxy)-2-nitrophenyl]-3-butynyl}-N-hydroxyurea
88				140 -145	539,2	4,12	N-{4-[4-(2-{4-[bis(4-fluorophenyl)methyl]-1-piperazinyl}ethoxy)phenyl]butyl}-N-hydroxyurea
89		CHIRAL R	Fumarate	162 - 165	576,2	3,14	5-{4-[(aminocarbonyl)(hydroxy)amino]-1-butynyl}-2-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}ethoxy)benzamide
90		CHIRAL R		70 - 75	577,9	4,17	N-{4-[4-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}ethoxy)-2-nitrophenyl]-3-butynyl}-N-hydroxyurea
91		CHIRAL R	Maleate	169 -172	576,2	3,14	5-{4-[(aminocarbonyl)(hydroxy)amino]-1-butynyl}-2-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}ethoxy)benzamide
92		CHIRAL R	L-tartrate	155 - 158	576,2	3,14	5-{4-[(aminocarbonyl)(hydroxy)amino]-1-butynyl}-2-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}ethoxy)benzamide

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
93		CHIRAL R	Citrate	153 - 156	576	3,14	5-{4-[(aminocarbonyl)(hydroxy)amino]-1-butynyl}-2-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}ethoxy)benzamide
94		CHIRAL R		64 - 66	538	4,39	N-{3-[4-(3-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}propyl)phenoxy]propyl}-N-hydroxyurea
95		CHIRAL R		127 - 130	557	4,44	N-(4-{4-[(4-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}-2-butynyl)oxy]phenyl}-3-butynyl)-N-hydroxyurea

Particularly preferred compounds are those listed in Table I, *infra*.

More preferred are compounds **1, 5, 11, 12, 13, 17, 23, 24, 31, 32, 33, 34, 35, 36, 37, 40, 41, 42, 43, 44, 45, 46, 48, 49, 50, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93,** and **94**.

The most preferred compounds are **17, 32, 34, 35, 46, 52** and **80**.

Definitions

The following paragraphs provide definitions of the various chemical moieties that make up the compounds of the invention and are intended to apply uniformly throughout the specification and claims unless expressly stated otherwise.

The term alkyl refers to a univalent C_1 to C_6 saturated straight, branched, or cyclic alkane moiety and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group can be optionally substituted with any appropriate group, including but not limited to R^3 or one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art or as taught, for example, in Greene, *et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Third Edition, 1999.

The term alkoxy refers to an alkyl moiety having a terminal –O- with free a valence, *e.g.*, CH_3CH_2-O-;

The term yloalkoxy is an alkoxy (as defined above) in which a hydrogen atom has been removed from the alkyl moiety to yield a divalent radical, *.e.g.*, -CH_2CH_2O- or –$CH(CH_3)O$-.

The term yloalkoxyalkyl refers to a divalent, dialkyl ether moiety having one free valence on each of the alkyl moieties, which alkyl moieties are the same or different, *e.g.*, -$CH_2CH_2CH_2$-O-CH_2-.

The term alkylene refers to an alkyl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, -$CH_2CH(CH_3)CH_2CH_2$-.

The term alkenyl refers to a univalent C_2-C_6 straight, branched, or in the case of C_{5-6}, cyclic hydrocarbon with at least one double bond, optionally substituted as described above.

The term alkenylene refers to an alkenyl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, -CH_2CH=$CHCH_2$-.

The term alkynyl refers to a univalent C_2 to C_6 straight or branched hydrocarbon with at least one triple bond (optionally substituted as described above) and specifically includes acetylenyl, propynyl, and -C≡C-CH_2(alkyl), including -C≡C-$CH_2(CH_3)$.

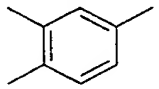
The term alkynylene refers to an alkynyl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, -C≡C-$CH(CH_3)$-.

The term aryl refers to a univalent phenyl (preferably), biphenyl, or napthyl. The aryl group can be optionally substituted with any suitable group, including but not limited to one or

more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Third Edition, 1999, and preferably with halo (including but not limited to fluoro), alkoxy (including methoxy), aryloxy (including phenoxy), W, cyano, or R^3.

The terms arylene and divalent arene refer to an aryl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, $-C_6H_4-$.

The term trivalent arene refers to an arylene moiety (as defined above) in which a hydrogen atom has been removed to yield a trivalent radical, *e.g.*,



The term yloalkylaryl refers to a divalent alkyl-substituted aryl moiety in which one open valence is on the alkyl moiety and one is on the aryl moiety, *e.g.*, $-CH_2-CH_2-C_6H_4-$.

The term yloarylalkyl refers to a divalent aryl-substituted alkyl moiety in which one open valence is on the alkyl moiety and one is on the aryl moiety, *e.g.*, $-C_6H_4-CH_2-CH_2-$.

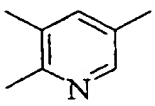
The term diylodialkylarene refers to a divalent, dialkyl-substituted arene in which there is one open valence on each of the alkyl moieties (which may be the same or different), *e.g.*, $-CH_2-C_6H_4-CH_2CH_2-$.

The term heteroatom means O, S, or N.

The term heterocycle refers to a cyclic alkyl, alkenyl, or alkynyl moiety as defined above wherein one or more ring carbon atoms is replaced with a heteroatom.

The terms heteroarylene and divalent heteroarene refer to an arylene (or divalent heteroarene) that includes at least one sulfur, oxygen, or nitrogen in the aromatic ring, which can optionally be substituted as described above for the aryl groups. Non-limiting examples are, furylene, pyridylene, 1,2,4-thiadiazolylene, pyrimidylene, thienylene, isothiazolylene, imidazolylene, tetrazolylene, pyrazinylene, pyrimidylene, quinolylene, isoquinolylene, benzothienylene, isobenzofurylene, pyrazolylene, indolylene, purinylene, carbazolylene, benzimidazolylene, and isoxazolylene.

The term trivalent heteroarene refers to a heteroarylene moiety (as defined above) in which a hydrogen atom has been removed to yield a trivalent radical, *e.g.*,



The term halo refers to chloro, fluoro, iodo, or bromo.

When a methylene of an alkyl, alkenyl, or alkynyl (or their divalent radical counterparts) is replaced by O, -NH-, -S-, -S(O)-, or $-S(O)_2-$, it may be at any suitable position in the moiety,

either at the terminal or internal positions, *e.g.*, CH_3CH_2-O-, CH_3-O-CH_2-, CH_3CH_2NH-, and CH_3NHCH_2-.

Open valences on the radical moieties described herein can occur on any one (or more for divalent radicals) of the atoms within the moiety. For example, the monovalent C_3 alkyl moiety includes both propyl and isopropyl. As another example, the divalent C_4 alkylene moiety includes both tetramethylene (-$CH_2(CH_2)_2CH_2$-) and ethylethylene (-$CH(CH_2CH_3)CH_2$-).

The term organic or inorganic anion refers to an organic or inorganic moiety that carries a negative charge and can be used as the negative portion of a salt.

The term "pharmaceutically acceptable cation" refers to an organic or inorganic moiety that carries a positive charge and that can be administered in association with a pharmaceutical agent, for example, as a countercation in a salt. Pharmaceutically acceptable cations are known to those of skill in the art, and include but are not limited to sodium, potassium, and quaternary ammonium.

The term "metabolically cleavable group" refers to a moiety that can be cleaved *in vivo* from the molecule to which it is attached, and includes but is not limited to an organic or inorganic anion, a pharmaceutically acceptable cation, acyl (for example (alkyl)C(O), including acetyl, propionyl, and butyryl), alkyl, phosphate, sulfate and sulfonate, $NH_2C(O)$- or (alkyl)OC(O)-.

The term 5-lipoxygenase inhibitor refers to a compound that inhibits the enzyme at 30 μM or lower. The term 15-lipoxygenase inhibitor refers to a compound that inhibits the enzyme at 30 μM or lower.

As used herein, the term pharmaceutically acceptable salts or complexes refers to salts or complexes that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as fumaric acid, maleic acid, acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include, but are not limited to the quaternary ammonium salt of the formula -NR^+Z^-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as fumarate, benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

The term pharmaceutically active derivative refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein.

Synthetic Schemes

The synthetic schemes displayed in Figs. 1-9 and Examples 1-7 illustrate how compounds according to the invention can be made. Those skilled in the art will be able to routinely modify and/or adapt these schemes and descriptions to synthesize any compound of the invention.

Pharmaceutical Compositions, Methods of Treatment and Administration

The compounds of the invention are useful for treating conditions in which there is likely to be a histamine and/or leukotriene component. These conditions include preferably asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media. The compounds exhibit this biological activity by acting as histamine H1 receptor antagonists, by inhibiting the lipoxygenase enzymes such as 5-lipoxygenase, or by exhibiting dual activity, *i.e.*, by acting as both a histamine H1 receptor antagonist and inhibitor of lipoxygenase such as 5-lipoxygenase.

Subjects in need of treatment for a leukotriene-mediated and/or histamine-mediated condition (preferably, asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media) can be treated by administering to the patient an effective amount of one or more of the above-identified compounds or a pharmaceutically acceptable derivative or salt thereof in a pharmaceutically acceptable carrier or diluent to reduce formation of oxygen radicals. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, intramuscularly or topically, in liquid, cream, gel or solid form, via a buccal or nasal spray, or aerosol.

The invention further concerns the use of the compounds of formula I for the manufacture of a medicament for therapeutic application. In particular, the invention concerns the use of the compounds of formula 1 for the manufacture of a medicament useful for treating conditions in which there is likely to be a histamine and/or leukotriene component. The invention concerns the use of the compound of formula 1 for the manufacture of a medicament useful for treating asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media, and preferably asthma, seasonal and perennial allergic rhinitis.

The invention further concerns the compounds of formula I for use as medicaments. The invention concerns the compounds of formula I for use as a medicament for treating asthma, seasonal and perennial allergic rhinitis, sinusitis, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media, and preferably asthma, seasonal and perennial allergic rhinitis.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

The methods of the invention comprise administration to a mammal (preferably human) suffering from a leukotriene-mediated and/or histamine-mediated condition (preferably, asthma and rhinitis) a pharmaceutical composition according to the invention in an amount sufficient to alleviate the condition. The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 1 to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. A oral dosage of 1–500, preferably 10-250, more preferably 25-250 mg is usually convenient.

The active ingredient should be administered to achieve peak plasma concentrations of the active compound of about 0.001–30 μM, preferably about 0.01–10 μM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterores; a glidant such

as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents.

The active compound or pharmaceutically acceptable salt or derivative thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active compound or pharmaceutically acceptable derivatives or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement, the desired action, such as adrenergic agonists like pseudoephedrine, antibiotics, antifungals, other anti-inflammatories, or antiviral compounds.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, intravenous, intramuscular or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation (CA) and Guilford Pharmaceuticals (Baltimore, Md.). Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidylcholine, arachadoyl phosphatidylcholine, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives are then introduced into the container. The container is then swirled by hand to free

lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

The following Examples are provided for illustrative purposes only and are not intended, nor should they be construed, as limiting the invention in any manner. Those skilled in the art will appreciate that routine variations and modifications of the following Examples can be made without exceeding the spirit or scope of the invention.

EXAMPLES

Example 1

Preparation of N-{[4-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl] methyl}-amino-N-hydroxyamide (compound 1, Figure 1)

4-(2-Bromoethoxy)benzylalcohol (compound **101**)

To a solution of 4-hydroxybenzylalcohol (2.0 g, 16.11 mmol) in DMF (10 mL) was added potassium carbonate (2.67 g, 19.32 mmol). The reaction was stirred at room temperature for 30 minutes and then 1,2-dibromoethane (3.03 g, 16.13 mmol) was added. The reaction was stirred at room temperature for additional 20 hours and then quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, evaporated to yield an oil which was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield **101** (1.7 g, 45.7%): ^{1}H NMR ($CDCl_3$) δ 3.64 (t, 2H), 4.29 (t, 2H), 4.62 (s, 2H), 6.91 (d, 2H), 7.30 (d, 2H).

4-{2-[4-((1R)(4-Chlorophenyl)phenylmethyl)piperazinyl]ethoxy}benzylalcohol (compound **103**)

To a solution of **101** (205 mg, 0.89 mmol), [(1R)(4-chlorophenyl) phenylmethyl]-piperazine (**102**) (230 mg, 0.80 mmol) in dichloromethane (2.5 mL) was added triethylamine (122.0 mg, 1.21 mmol). The reaction was stirred at 50° C for 20 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield **103** (330 mg, 94.1%): ^{1}H NMR ($CDCl_3$) δ 2.45 (m, 4H), 2.62 (m, 4H), 2.81 (t, 2H), 4.08 (t, 2H), 4.22 (s, 1H), 4.51 (s, 2H), 6.87 (d, 2H), 7.28 (m, 6H), 7.39 (m, 5H).

N-{[4-(2-{4-[(1R)(4-Chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}phenoxy-carbonylaminophenoxyformate (compound **104**)

To a stirred solution of **103** (330 mg, 0.76 mmol), phenoxycarbonylamino-phenoxyformate (251.6 mg, 0.92 mmol) and triphenylphosphine (225.2 mg, 0.86 mmol) in THF (8 mL) at 0° C was added diisopropylazodicarboxylate (174.1 mg, 0.86 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **104** (410 mg, 78.4%): ^{1}H NMR ($CDCl_3$) δ 2.47 (m, 4H), 2.65

(m, 4H), 2.84 (t, 2H), 4.12 (t, 2H), 4.23 (s, 1H), 4.95 (s, 2H), 6.92 (d, 2H), 7.20 (m, 5H), 7.26 (m, 6H), 7.40 (m, 10H).

N-{[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}-amino-N-hydroxyamide (compound 1)

In a screw top vessel was placed a solution of **104** (410 mg, 0.59 mmol) in methanol (15 mL) and cooled to -78° C with dry ice-acetone bath. To this vessel was added liquid NH_3 (2-3 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the pressure released. The vessel was opened and the solvent was evaporated. Compound **1** was separated by flash column chromatography (silica gel, 19:1 CH_2Cl_2/CH_3OH) (215 mg, 73.2%): ^1H NMR ($CDCl_3$) δ 2.42 (m, 4H), 2.59 (m, 4H), 2.74 (t, 2H), 3.98 (t, 2H), 4.20 (s, 1H), 4.57 (s, 2H), 5.22 (bs, 2H), 6.77 (d, 2H), 7.25 (m, 6H), 7.36 (m, 5H).

Example 2

Preparation of N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]but-3-ynyl}-amino-*N-hydroxyamide (compound 12, Figure 2)*

4-(2-Bromoethoxy)-1-iodobenzene (compound **105**)

To a solution of 4-iodophenol (10.0g, 45.45 mmol) in DMF (50 mL) was added potassium carbonate (12.6 g, 91.17 mmol). The reaction was stirred at room temperature for 30 minutes and then 1,2-dibromoethane (17.07 g, 90.91 mmol) was added. The reaction was stirred at room temperature for additional 16 hours and then quenched with water and extracted with dichloromethane. The organic layer was washed with water and brine, evaporated to yield an oil which was purified by flash column chromatography (silica gel, hexane) to yield **105** (2.7 g, 18.2%): ^1H NMR ($CDCl_3$) δ 3.63 (t, 2H), 4.26 (t, 2H), 6.70 (d, 2H), 7.58 (d, 2H).

4-[4-(2-Bromoethoxy)phenyl]but-3-yn-1-ol (compound **106**)

To a mixture of **105** (2.7 g, 8.26 mmol), 3-butyn-1-ol (696.3 mg, 9.94 mmol), dichlorobis(triphenylphosphine)palladium(II) (1.15 g, 1.64 mmol) and cuprous iodide (317.1 mg, 1.67 mmol) was added triethylamine (45 mL). The reaction was stirred at room temperature for 16 hours. The solvent was evaporated and the residue purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield **106** (1.3 g, 58.6%): ^1H NMR ($CDCl_3$) δ 2.70 (m, 4H), 3.65 (t, 2H), 3.82 (m, 2H), 4.30 (t, 2H), 6.83 (d, 2H), 7.37 (d, 2H).

4-{4-[2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy] phenyl} but-3-yn-1-ol (compound **107**)

To a solution of **106** (1.5 g, 5.58 mmol), [(1R)(4-chlorophenyl)phenylmethyl]piperazine (**102**) (1.6 g, 5.59 mmol) in DMF (15 mL) was added triethylamine (871.2 mg, 8.63 mmol). The reaction was stirred at 50° C for 20 hours, water was added, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated to an oil which was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to yield **107** (2.6 g, 98.1%): ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 4H), 2.61 (m, 4H), 2.68 (t, 2H), 2.82 (t, 2H), 3.80 (t, 2H), 4.10 (t, 2H), 4.21 (s, 1H), 6.80 (d, 2H), 7.26 (m, 5H), 7.35 (m, 6H).

N-{4-[4-(2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy) phenyl] but-3-ynyl} phenoxycarbonylaminophenoxyformate (compound **108**)

To a stirred solution of **107** (1.5 g, 3.16 mmol), phenoxycarbonylaminophenoxyformate (1.05 g, 3.85 mmol) and triphenylphosphine (937.1 mg, 3.57 mmol) in THF (35 mL) at 0° C was added diisopropylazodicarboxylate (721.4 mg, 3.57 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **108** (1.4 g, 60.6%): ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 4H), 2.62 (m, 4H), 2.82 (m, 2H), 2.91 (t, 2H), 4.10 (m, 4H), 4.21 (s, 1H), 6.80 (d, 2H), 7.18 (m, 5H), 7.30 (m, 8H), 7.37 (m, 8H).

N-{4-[4-(2-{4-[(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl] but-3-ynyl}-amino-N-hydroxyamide (compound **12**)

In a screw top vessel was placed a solution of **108** (1.4 g, 1.92 mmol) in methanol (50 mL) and cooled to -78° C with dry ice-acetone bath. To this vessel was added liquid NH_3 (6 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the pressure released. The vessel was opened and the solvent evaporated. Compound **12** was separated by flash column chromatography (silica gel, 19:1 CH_2Cl_2/CH_3OH) (580 mg, 56.9%): ^{1}H NMR ($CDCl_3$) δ 2.45 (m, 4H), 2.65 (m, 4H), 2.72 (t, 2H), 2.84 (t, 2H), 3.80 (t, 2H), 4.10 (t, 2H), 4.22 (s, 1H), 5.25 (bs, 2H), 6.80 (d, 2H), 7.25 (m, 5H), 7.36 (m, 6H).

Example 3

Preparation of N-{4-[4-(2-{4-[(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl]butyl}-amino-N-hydroxyamide (compound 17, Figure 3)

4-[4-(2-Bromoethoxy)phenyl]butan-1-ol (compound **109**)

A solution of **106** (1.3 g, 4.83 mmol) in methanol (15 mL) was hydrogenated over 10% palladium on charcoal (130 mg) at balloon pressure for 7 hours. The catalyst was filtered off and the filtrate was evaporated to give **109** (1.31 g, 99.2%): ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.60 (t, 2H), 3.66 (m, 4H), 4.28 (m, 2H), 6.83 (d, 2H), 7.10 (d, 2H).

4-{4-[2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy] phenyl} butan-1-ol (compound **110**)

To a solution of **109** (1.3 g, 4.76 mmol) and [(1R)(4-chlorophenyl)phenylmethyl]piperazine (**102**) (1.39 g, 4.86 mmol) in DMF (12 mL) was added triethylamine (762.3 mg, 7.55 mmol). The reaction was stirred at 50° C for 16 hours, water was added, and the reaction was extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered, and evaporated to an oil, which was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to yield **110** (2.42 g, 104%): ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.45 (m, 4H), 2.62 (m, 6H), 2.81 (t, 2H), 3.66 (t, 2H), 4.08 (t, 2H), 4.21 (s, 1H), 6.81 (d, 2H), 7.08 (d, 2H), 7.25 (m, 4H), 7.36 (m, 5H), 8.02 (bs, 1H).

N-{4-[4-(2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy) phenyl] butan-1-ol} phenoxycarbonylaminophenoxyformate (compound **111**)

To a stirred solution of **110** (1.5 g, 3.14 mmol), phenoxycarbonylaminophenoxyformate (1.05 g, 3.85 mmol) and triphenylphosphine (938.0 mg, 3.58 mmol) in THF (35 mL) at 0° C was added diisopropylazodicarboxylate (724.0 mg, 3.58 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **111** (1.58 g, 68.7%).

N-{4-[4-(2-{4-[(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl] butyl}-amino-N-hydroxyamide (compound **17**)

In a screw top vessel was placed a solution of **111** (1.58 g, 2.16 mmol) in methanol (50 mL) and cooled to -78° C in a dry ice-acetone bath. To this vessel was added liquid ammonia (6 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the

pressure was released. The vessel was opened and the solvent was evaporated. Compound **17** was separated by flash column chromatography (silica gel, 19:1 CH_2Cl_2/CH_3OH) and further purified by recrystallization using ethyl acetate-hexane as a solvent (550 mg, 47.4%): ^1H NMR ($CDCl_3$) δ 1.60 (m, 4H), 2.44 (m, 4H), 2.52 (t, 2H), 2.67 (m, 4H), 2.83 (t, 2H), 3.48 (t, 2H), 4.08 (t, 2H), 4.21 (s, 1H), 6.78 (d, 2H), 7.04 (d, 2H), 7.25 (m, 4H), 7.35 (m, 5H).

Example 4

Preparation of methyl-2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzoate (compound 36, Figure 4), 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino) but-1-ynyl] benzamide (compound 35, Figure 4), and 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl} ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzoic acid (compound 37, Figure 5)

4-iodophenol, methyl acetate (compound **112**)

To a solution of 5-iodosalicylic acid (5.0 g, 18.94 mmol) in methanol (100 mL) was added a few drops of sulfuric acid. The reaction was stirred at reflux for 24 hours. The reaction solvent (methanol) was evaporated to small volume and water was added and extracted with dichloromethane. The organic layer was washed with 10% $NaHCO_3$ solution, water and brine, dried over magnesium sulfate, filtered and evaporated to give the title compound (3.5 g, 66.5%): ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 6.78 (d, 1H), 7.70 (dd, 1H), 8.12 (d, 1H).

Methyl 2-hydroxy-5-(4-hydroxybut-1-ynyl)benzoate (compound **113**)

To a mixture of **112** (2.0 g, 7.19 mmol), 3-butyn-1-ol (655.2 mg, 9.35 mmol), dichlorobis(triphenylphosphine)palladium(II) (1.0 g, 1.42 mmol) and cuprous iodide (276.3 mg, 1.45 mmol) was added triethylamine (40 mL). The reaction was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to yield **113** (1.6 g, 101.3%): ^1H NMR ($CDCl_3$) δ 2.68 (t, 2H), 3.81 (m, 2H), 3.96 (s, 3H), 6.92 (d, 1H), 7.50 (dd, 1H), 7.93 (d, 1H).

Methyl 2-(2-bromoethoxy)-5-(4-hydroxybut-1-ynyl)benzoate (compound **114**)

To a solution of **113** (1.6 g, 7.27 mmol) in DMF (8 mL) was added potassium carbonate (1.51 g, 10.91 mmol). The reaction was stirred at room temperature for 30 minutes and then 1,2-dibromoethane (5.47 g, 29.09 mmol) was added. The reaction was stirred at room temperature for additional 16 hours and then quenched with water and extracted with dichloromethane. The organic layer was washed with water and brine, evaporated to yield an oil which was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to yield **114** (710 mg, 29.8%):

^{1}H NMR ($CDCl_3$) δ 2.70 (t, 2H), 3.68 (t, 2H), 3.82 (t, 2H), 3.90 (s, 3H), 4.35 (t, 2H), 6.90 (d, 1H), 7.50 (dd, 1H), 7.88 (d, 1H).

Methyl 2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy)-5-(4-hydroxybut-1-ynyl)benzoate (compound **115**)

To a solution of **114** (300.0 mg, 0.92 mmol), [(1R)(4-chlorophenyl) phenylmethyl] piperazine (**102**) (262.4 mg, 0.92 mmol) in DMF (2 mL) was added triethylamine (139.0 mg, 1.38 mmol). The reaction was stirred at 50° C for 20 hours, water was added, and the reaction was extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated to an oil which was purified by flash column chromatography (silica gel, ethyl acetate) to yield **115** (510 mg, 102.4%): ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 4H), 2.68 (m, 6H), 2.90 (m, 2H), 3.81 (t, 2H), 3.84 (s, 3H), 4.08 (m, 2H), 4.21 (s, 1H), 6.90 (d, 1H), 7.25 (m, 4H), 7.38 (m, 5H), 7.49 (dd, 1H), 7.85 (d, 1H).

N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-3-(methoxycarbonyl) phenyl] but-3-ynyl} phenoxycarbonylamino phenoxyformate (compound **116**)

To a stirred solution of **115** (320.0 mg, 0.60 mmol), phenoxycarbonylaminophenoxyformate (198.4 mg, 0.73 mmol) and triphenylphosphine (55.7 mg, 0.21 mmol) in THF (2 mL) at 0° C was added diisopropylazodicarboxylate (78.2 mg, 0.68 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **116** (350 mg, 73.9%): ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 4H), 2.65 (m, 6H), 2.90 (m, 2H), 3.82 (s, 3H), 4.15 (m, 4H), 4.21 (s, 1H), 6.85 (d, 1H), 7.25 (m, 8H), 7.40 (m, 12H), 7.82 (s, 1H).

Methyl 2- (2- {4- [(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) -5- [4-(aminohydroxycarbonyl amino)but-1-ynyl]benzoate (compound **36**) and 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonyl amino)but-1-ynyl]benzamide (compound **35**)

In a screw top vessel was placed a solution of **116** (350 mg, 0.44 mmol) in methanol (20 mL) and cooled to -78°C in a dry ice-acetone bath. To this vessel was added liquid ammonia (3 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the pressure released. The vessel was opened and the solvent was evaporated. Compound **36** was separated by flash column chromatography (silica gel, 9:1 CH_2Cl_2/CH_3OH) as a white solid. The mixture of compound **35** and **36** was further purified by flash column chromatography (silica gel, 9:1 CH_2Cl_2/CH_3OH) to give additional compound **36** (total 31 mg) and compound **35** (containing

about 5% compound **36**). Compound **35** was further separated from compound **36** by recrystallization using ethyl acetate-hexane as a solvent (35 mg).

Compound **36**: ^{1}H NMR ($CDCl_3$) δ 2.45 (m, 4H), 2.70 (m, 6H), 2.90 (t, 2H), 3.75 (t, 2H), 3.83 (s, 3H), 4.18 (t, 2H), 4.21 (s, 1H), 5.34 (bs, 2H), 6.85 (d, 1H), 7.25 (m, 4H), 7.37 (m, 5H), 7.43 (dd, 1H), 7.80 (s, 1H).

Compound **35**: ^{1}H NMR ($CDCl_3$) δ 2.40 (m, 4H), 2.54 (m, 4H), 2.75 (t, 2H), 2.80 (t, 2H), 3.80 (t, 2H), 4.20 (m, 3H), 5.42 (bs, 2H), 5.80 (bs, 1H), 6.87 (d, 1H), 7.25 (m, 4H), 7.36 (m, 5H), 7.45 (dd, 1H), 8.14 (d, 1H), 8.75 (bs, 1H).

2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonyl-amino)but-1-ynyl] benzoic acid (compound 37)

In a small round-bottomed flask was placed compound **36** (30 mg, 0.05 mmol). To this flask was added 1M KOH/CH_3OH (0.30 mL, 0.30 mmol). The reaction was stirred at room temperature for 48 hours and then cooled in an ice bath. 1M HCl/ether (0.30 mL, 0.30 mmol) was added and the mixture was purified by flash column chromatography (silica gel, 9:1 CH_2Cl_2/CH_3OH) to give **37** as a white solid (9 mg, 31.4%): ^{1}H NMR (CD_3OD) δ 2.56 (m, 4H), 2.66 (t, 2H), 2.96 (m, 4H), 3.10 (t, 2H), 3.68 (t, 2H), 4.32 (t, 2H), 4.34 (s, 1H), 6.98 (d, 1H), 7.20 (d, 1H), 7.30 (m, 4H), 7.44 (m, 6H).

Example 5

Preparation of Amino N-{4-[4-(2-{4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl}ethoxy)phenyl]but-3-ynyl}-N-hydroxyamide (compound 32, Figure 7)

4-(2-Bromoethoxy)-1-iodobenzene

To a stirring solution of 4-iodophenol (25g, 110 mmol) and K_2CO_3 (31 g, 220 mmol) in DMF (250 mL) was added 1,2-dibromoethane (5 mL, 55 mmol) over a period of 1hr. The solution was heated at 50°C and stirred overnight under Ar. In order to complete the reaction additional reagents were added: 1,2-dibromoethane (20 mL, 220 mmol) and K_2CO_3 (6 g, 43 mmol) and the mixture was heated at 50°C an additional 12 hours under Ar. Water was added and the reaction mixture was extracted with dichloromethane, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude mixture was purified by silica gel chromatography eluted with 10% ethyl acetate in hexanes to give the title compound as a white solid (5.5 g, 17mmol).

4-[4-(2-Bromoethoxy)phenol]but-3-yn-1-ol

To a mixture of 4-(2-Bromoethoxy)-1-iodobenzene (5.5 g, 17 mmol), 3-butyn-1-ol (1.9 mL, 25 mmol), CuI (952mg, 5 mmol) and dichlorobis(triphenylphosphine)palladium(II) (3.5 g, 5

mmol) in dichloromethane (100mL) was added dropwise Et_3N (3.5 mL, 25mmol). The reaction was stirred overnight at room temperature under Ar. The solvent was evaporated under reduced pressure and ethyl acetate was added to dissolve the reaction mixture, which was filtered over celite to remove most of the Pd. The crude product was purified by silica gel chromatography eluted with hexane/ethyl acetate (2:1). 4 g of the title compound were obtained as a light brown solid.

4-[4-(2-{4-(8-chloro-5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-yliden)piperidyl}ethoxy)but-3-yn-1ol

8-chloro-11-(4-piperidylidene)-5,6-dihydrobenzo[a]pyridino[2,3-d][7]annulene (2.5 g, 7.75 mmol) and 4-[4-(2-bromoethoxy)phenol]but-3-yn-1-ol (2.5 g, 9.2 mmol) were disolved in dichloromethane. To this solution was added Et_3N (2.6 mL, 18.5 mmol) and the reaction was heated at reflux overnight under Ar. The dichloromethane was evaporated under reduced pressure. The unreacted starting materials were recovered after purification by chromatography with 10% MeOH in dichloromethane. The title compound was obtained as a white solid (1.9 g, 3.76 mmol).

Phenyl{N-{4-[4-(2-{4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl}ethoxy)phenyl]but-3-ynyl}phenoxycarbonylaminooxy}formate

A solution of 4-[4-(2-{4-(8-chloro-5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-yliden)piperidyl}ethoxy)but-3-yn-1ol (1.9 g, 3.76 mmol), triphenylphosphine (1.2 g, 4.7 mmol) and N,O-bis-(phenoxycarbonyl)hydroxylamine (1.3 g, 4.7 mmol) in THF (20 mL) was cooled at 0°C with an ice bath. Diisopropylazodicarboxlate (950 mg, 4.7 mmol) was added dropwise to the stirring solution. The reaction was allowed to warm to room temperature and stir for one hour. Once the reaction was complete, the solvent was evaporated under vacuum. The product was purified by silica gel chromatography using 10% MeOH in dichloromethane. 4;5 g of the title compound (slightly impure) were obtained.

Amino-N-{4-[4-(2-{4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl}ethoxy)phenyl]but-3-ynyl}-N-hydroxyamide

Phenyl{N-{4-[4-(2-{4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl}ethoxy)phenyl]but-3-ynyl}phenoxycarbonylaminooxy}formate (4.5 g) was disolved in MeOH saturated with NH_3 (100mL). The system was sealed with a rubber septum and the mixture was stirred at room temperature overnight. The the solvent was evaporated under vacuum and the crude compound was purified by chromatography on silica gel, eluted with 10%

MeOH saturated with NH_3 in dichloromethane to give the title compound, compound **32** (800 mg) [Alternatively, the reaction may be run in a pressure tube].

Example 6

Preparation of N-{4-[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}propoxy)phenyl]but-3-ynyl}-amino-N-hydroxyamide (compound 52)

4-(2-Bromopropoxy)-1-iodobenzene

To a stirring solution of 4-iodophenol (15 g, 70 mmol) and K_2CO_3 (12.4 g, 90 mmol) in DMF (30 mL) was added 1,2-dibromopropane (7.8 mL, 90 mmol) over a period of 1hr. The solution was heated at 50°C and stirred overnight under Ar. Water (500 mL) was added and the reaction mixture was extracted with dichloromethane, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. Purified on silica gel chromatography, eluted with 10% ethyl acetate in hexanes to give the title compound as a white solid (10 g, 29mmol).

4-[4-(2-Bromopropoxy)phenyl]but-3-yn-1-ol

To a solution of 4-(2-Bromopropoxy)-1-iodobenzene (10 g, 29 mmol), 3-butyn-1-ol (2.6 mL, 37 mmol), CuI (980 mg, 5.2 mmol) and dichlorobis(triphenylphosphine)palladium(II) (3.6 g, 5.2 mmol) in dichloromethane (40mL) was added Et_3N (6.0 mL, 44 mmol) dropwise. The reaction was stirred overnight at room temperature under Ar. The solvent was evaporated under reduced pressure and ethyl acetate was added to dissolve the compound, the solution was filtered over celite to remove most of the Pd. The crude product was purified by silica gel chromatography, eluted with hexane/ethyl acetate (2:1). 2.6 g of the title compound were obtained as a light brown solid

4-{4-[3-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) propoxy] phenyl} but-3-yn-1-ol

[(1R)(4-chlorophenyl)phenylmethyl]piperazine (1.6 g, 5.6 mmol) and 4-[4-(2-bromopropoxy)phenyl]but-3-yn-1-ol (2.0 g, 7.04 mmol) were dissolved in dichloromethane (10 mL). Et_3N (1 mL, 7.04 mmol) was added dropwise, the solution was heated at reflux under Ar overnight. The solvent was evaporated and the compound was purified by silica gel chromatography, eluted with ethyl acetate. 2.0 g of the title compound were obtained as a white solid.

N-{4-[4-(3-(4-((1R) (4-chlorophenyl) phenylmethyl) piperazinyl) propoxy) phenyl] but-3-ynyl} phenoxycarbonylaminophenoxyformate

A solution of 4-{4-[3-(4-((1R) (4-chlorophenyl) phenylmethyl) piperazinyl) propoxy] phenyl} but-3-yn-1-ol (1.6 g, 5.6 mmol), triphenylphosphine (1.3 g, 5.1 mmol) and N,O-bis-(phenoxycarbonyl)hydroxylamine (1.4 g, 5.1 mmol) in THF (20 mL) was cooled at 0°C with an ice bath. Diisopropylazodicarboxlate (1.0 g, 5.1 mmol) was added dropwise to the stirring solution. Then the reaction was allowed to warm to room temperature and stir for one hour. After completion of the reaction, the solvent was evaporated under vacuum. No further purification of the compound was done.

N-{4-[4-(2-{4-[(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} propoxy) phenyl] but-3-ynyl}-Amino-N-hydroxyamide (compound **52**)

N-{4-[4-(3-(4-((1R) (4-chlorophenyl) phenylmethyl) piperazinyl) propoxy) phenyl] but-3-ynyl} phenoxycarbonylaminophenoxyformate was dissolved in MeOH and added to 20 mL of condensed (dry ice/acetone) NH_3 in a pressure tube. The pressure tube was closed, allowed to warm at room temperature. After stirring overnight, the pressure was released slowly and the cap removed opening the system to the air, then the solvent was evaporated under vacuum. Purification by silica gel chromatography, eluted with 10% MeOH saturated with NH_3 in dichloromethane afforded the title compound, compound **52** (1.05 g)

Example 7

*Preparation of Amino-N-{4-[4-(4-{4-[bis(4 fluorophenyl)methyl]piperazinyl}butoxy) phenyl]but-3-ynyl}-N-hydroxyamide (compound **80**, Figure 6)*

1-(4-bromobutoxy)-4-iodobenzene (**117**). To a stirring solution of 4-iodophenol (100g, 0.5 mol) and K_2CO_3 (70 g, 0.5 mol) in DMF (400 mL) was added 1,4 dibromobutane (100 mL, 0.84 mol) over a period of 1 hr. The solution was stirred overnight at room temperature under Ar. H_2O (1000 mL) was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was then washed with 1000 mL of brine, dried over $MgSO_4$, concentrated to gave a white solid (100 g); ^1H NMR (CD_3Cl): δ 2.15 – 1.87 (m, 6H), 3.50 – 3.20 (m, 4H), 3.94 (t, 2H), 6.85 (d, 2H), 7.55 (d, 2H).

4-[4-(4-bromobutoxy)phenol]but-3-yn-1-ol (**118**). A solution of **117** (100 g, 0.3 mol), 3-butyn-1-ol (45 mL, 0.6 mol), CuI (800 mg, 4.2 mmol) and dichlorobis (triphenylphosphine) palladium (II) (2.9 g, 4.2 mmol) in dichloromethane (400 mL) was cooled at 0 C (ice bath). Et_3N

(84 mL, 0.6 mol) was added dropwise while maintaining the low temperature. Then the mixture was warmed at room temperature and stirred overnight under Ar. The dichloromethane was removed under vacuum. The semi-solid obtained, was dissolved in a minimum of CH_2Cl_2 and passed over a large plug of silica gel eluting with 10% EtOAc in hexane, followed by 50% EtOAc : 50% hexane. 75 g of a light tan solid were obtained; ^{1}H NMR (CD_3Cl) δ 2.10 – 1.80 (m, 4H), 2.66 (t, 2H), 3.25 (t, 1H), 3.50 (t, 2H), 3.80 (t, 2H), 3.94 (t, 2H), 6.85 (d, 2H), 7.55 (d, 2H).

Compound **119**: 4-bis(4-fluorophenyl methyl piperazine (58 g, 0.2 mol) and **118** (74 g, 0.25 mol) were dissolved in CH_2Cl_2 (500 mL). To this solution was added NEt_3 (43 mL, 0.31 mol). The mixture was allowed to stir for 48 hr at room temperature under Ar. After evaporation of the solvent under vacuum, the semi-solid obtained was dissolved in a minimum amount of CH_2Cl_2 and passed over a large plug of silica gel eluting with 50% EtOAc:50% hexane, followed by EtOAc to remove the desired compound. Concentration of the solution gave an off-white foam (70 g) 90% pure; ^{1}H NMR (CD_3Cl) δ 1.78 – 1.75 (m, 6H), 2.72 – 2.45 (m, 12H), 3.78 (t, 2H), 3.94 (t, 2H), 4.23 (s, 1H), 6.76 (d, 2H), 6.97 (t, 4H), 7.37 –7.25 (m, 6H).

Compound **80**: A solution of **119** (70 g, 0.14 mol), triphenylphosphine (45 g, 0,17 mol) and N,O-bis-(phenoxycarbonyl)hydroxylamine (46 g, 0.17 mol) in THF (500 mL) was cooled at 0°C with an ice bath. Diisopropylazodicarboxylate (34 mL, 0.17 mol) was added dropwise to the stirring solution. The ice bath was removed, the reaction was allowed to warm at room temperature and stir for 1 hr. The reaction was checked by TLC for completion. The solvent was removed under vacuum, the crude material was dissolved in 700 mL of MeOH saturated with ammonia. The mixture was stirred overnight in a round bottom flask sealed with a rubber septa. The reaction was worked up by an acid/base extraction, concentrated and passed over a large plug of silica gel (45 g), eluted with 10% MeOH in dichloromethane. The product was recrystallized with 500 mL of refluxing EtOAc, and cooled at room temperature overnight to gave 20 g pure compound; ^{1}H NMR (CD_3Cl) δ 1.78 – 1.75 (m, 6H), 2.57 – 2.45 (m, 10H), 2.72 (t, 2H), 3.78 (t, 2H), 3.94 (t, 2H), 4.23 (s, 1H), 5.34 (s br, 2H), 6.76 (d, 2H), 6.97 (t, 4H), 7.37 –7.25 (m, 6H).
The following Table II provides illustrative NMR data for the especially preferred compounds.

TABLE II

COMPOUND #	^{1}H-NMR ($CDCl_3$) δ (ppm)
17	1.60 (m, 4H), 2.44 (m, 4H), 2.52 (t, 2H), 2.67 (m, 4H), 2.83 (t, 2H), 3.48 (t, 2H), 4.08 (t, 2H), 4.21 (s, 1H), 6.78 (d, 2H), 7.04 (d, 2H), 7.25 (m, 4H), 7.35 (m, 5H).
32	2.20-2.95 (m, 14H), 3.35 (m, 2H), 3.72 (t, 2H), 4.05 (t, 2H), 5.62 (brs, 2H), 6.72 (d, 2H), 7.10 (m, 4H), 7.25 (d, 2H), 7.45 (d, 1H), 8.35 (d, 1H).
34	2.45 (br d, 8H); 2.75 (t, 2H); 3.50 (s, 2H); 3.70 (t, 2H); 4.20 (s, 1H); 5.57 (br s, 2H); 6.15 (d, 1H); 6.39 (d, 1H); 6.95 (t, 4H); 7.33 (dd, 4H).
35	2.40 (m, 4H), 2.54 (m, 4H), 2.75 (t, 2H), 2.80 (t, 2H), 3.80 (t, 2H), 4.20 (m, 3H), 5.42 (br s, 2H), 5.80 (br s, 1H), 6.87 (d, 1H), 7.25 (m, 4H), 7.36 (m, 5H), 7.45 (dd, 1H), 8.14 (d, 1H), 8.75 (br s, 1H).
46	1.40-1.55 (m, 1H); 1.85-1.96 (m, 1H); 2.05-2.20 (m, 2H); 2.30-2.70 (m, 12H); 3.62 (ddd, 2H); 4.18 (s, 1H); 4.27 (br d, 1H); 4.63 (br t, 1H); 5.58 (br s, 2H); 7.15-7.35 (m, 9H).
52	1.95 (m, 2H), 2.65-2.35 (m, 10H), 2.72 (t, 2H), 3.78 (t, 2H), 3.93 (t, 2H), 4.20 (s, 1H), 5.25 (brs, 2H), 6.75 (d, 2H), 7.15-7.40 (m, 11H).
80	1.78 – 1.75 (m, 6H), 2.57 – 2.45 (m, 10H), 2.72 (t, 2H), 3.78 (t, 2H), 3.94 (t, 2H), 4.23 (s, 1H), 5.34 (s br, 2H), 6.76 (d, 2H), 6.97 (t, 4H), 7.37 –7.25 (m, 6H).

Example 8

CHO-K1 H1R Binding Assay Protocol

This assay is commonly used to measure the ability of a compound to act as a histamine H1 receptor binding ligand. As this assay employs human cloned H1 receptors it can provide a good approximation of what can be expected when a compound is administered to humans.

Details of the assay procedure are as follows. CHO-K1 cells expressing the human cloned H1 receptor are grown to confluence in tissue culture dishes. Cells are harvested using D-PBS buffer (JRH Biosciences), kept at 4°C, centrifuging to pellet cells (4°C, 500g, 10 min). The final

cell pellet is homogenized and resuspended using Tris/sucrose buffer (20 mM Tris, 250 mM sucrose, pH 7.4 at 4°C). Aliquots of the membrane preparation are stored at -70 °C.

On the day of assay, the membrane preparation is thawed and centrifuged (TLA100.3 rotor, 4°C, 15 min, 23,000 rpm). The pellet is resuspended in Tris/sucrose buffer initially and then diluted further as necessary using assay buffer A (50 mM Na/KPO_4, 2 mM $MgCl_2$, 0.5% (w/v) BSA, pH 7.5).

For the binding assay, the membrane preparation, test compound and ^3H-pyrilamine (2 nM final) in buffer A with 1% (v/v) DMSO final are incubated in a 96-well polypropylene plate for 3 hours at 37°C. Non-specific binding is determined in the presence of 10 µM pyrilamine. A 96-well harvester (Packard) is used to harvest the 96-well plate onto a GF/B filter plate pre-treated with 0.1% (v/v) PEI. The plate is counted in a Packard Topcounter after adding Microscint 20 (Packard) scintillation fluid. The K_i for each compound at the histamine H1 receptor is then calculated from these counts. The results are displayed in Table 1, *infra*.

Example 9

Inhibition of LTB_4 Production in Human Whole Blood

This assay examines the ability of a compound to inhibit leukotriene B_4 production from human blood stimulated with calcium ionophore. As this production of leukotriene B_4 is mediated via the activation of the 5-lipoxygenase enzyme, this assay is predictive of a compound's ability to inhibit the human 5-lipoxygenase enzyme.

The procedure for the assay is as follows. Blood is drawn from normal human volunteers into tubes containing heparin. 1 ml of the heparinized blood is pipetted into a 1.5 ml polypropylene tube. To this sample is added either different concentrations of the test compound (5 µl) dissolved in DMSO or 5 µl of DMSO as a vehicle control. These samples are incubated in a water bath, at 37°C for 15 min. 5 µl of the calcium ionophore A23187 (at a final concentration of 50 µM) is then added to each sample, which is vortexed and placed back in the water bath for 30 min. The samples are then centrifuged at 2500 rpm for 10 min. at 4°C. 50 µl of the supernatant is transferred into pre-cooled Eppendorf tubes containing 950 µl of enzyme immunoassay (EIA) buffer. A commercially available EIA kit (Cayman Chemical Co., Ann Arbor, MI, USA) is used to subsequently measure the LTB4 production in the samples. The LTB_4 levels produced in the vehicle control sample is then compared to those in which the test compound has been added. From this a percent inhibition of LTB_4 production by each concentration of test compound is calculated and the IC_{50} for inhibition of LTB_4 production for each test compound is determined. The results are displayed in Table 1, *infra*.

Table 1

Cpd #	CHOH1 K_I (nM)	HWB IC_{50} (nM)
1	24	1515
3	260	1681
5	23	2041
46	133	313
8	220	5768
9	12	4222
11	130	3626
12	380	267
80	27	78
13	10	2444

Cpd #	CHOH1 K_I (nM)	HWB IC_{50} (nM)
16	94	2657
87	58	251
18	15	2101
22	8	1473
23	10	287
24	7	253
26	4	1714
27	150	650
30	36	412
17	15	254

Cpd #	CHOH1 K_I (nM)	HWB IC_{50} (nM)
32	7	263
34	550	142
35	135	85
36	420	94
37	4	6589
40	120	122
42	35	106
52	6	105
43	2	2742

Example 10

Antihistaminergic Activity In Vivo

Male, Hartley guinea pigs are obtained from Charles River Labs at a body weight of 350 - 400 grams. Inhibition of histamine activity is measured by the method of Konzett and Rössler (*Naonyn-Schmiedebergs Arch. Exp. Path. Pharmakol.* **195**, 71-74 (1940). Anaesthetized guinea pigs are subjected to artificial ventilation. The endotracheal pressure is recorded. Bronchoconstriction is induced by successive intravenous injections of histamine. The test compounds are administered orally in a 1% methocellulose suspension at set timepoints prior to the administration of histamine.

The results (Table 2) show the percent inhibition of histamine-induced bronchoconstriction by selected compounds at multiple time points post oral dosing. 50% inhibition or greater is considered significant.

Table 2

Cpd #	Dose of test cpd	Time (in hours)	% inhibition
1	5mg/kg	3 hrs	56%
12	2 mg/kg	3 hrs	62%
12	2 mg/kg	6 hrs	66%
87	2 mg/kg	3 hrs	66%
87	2 mg/kg	6 hrs	73%
23	2 mg/kg	3 hrs	80%
23	2 mg/kg	6 hrs	92%
27	2 mg/kg	3 hrs	86%
27	2 mg/kg	6 hrs	91%
32	2 mg/kg	3 hrs	65%
34	2 mg/kg	3 hrs	81%
34	2 mg/kg	6 hrs	89%
17	2 mg/kg	3 hrs	66%
17	2 mg/kg	6 hrs	73%
35	2 mg/kg	3 hrs	72%
35	2 mg/kg	6 hrs	88%
52	2 mg/kg	3 hrs	69%
80	2 mg/kg	3 hrs	98%

It can be seen from this Table that compounds of the present invention possess good activity with regard to their ability to inhibit histamine-induced bronchoconstriction. Furthermore, several of the compounds administered at a single dose possess antihistaminergic activity of long duration. For example, **27**, at a dose of 2 mg/kg, still inhibits histamine-induced bronchoconstriction by 91% at 6 hours post oral dosing.

These experiments also indicate that the compounds tested are orally bioavailable.

Example 11

5-Lipoxygenase Inhibitory Activity in vivo

Male, Hartley guinea pigs are obtained from Charles River Labs at a body weight of 350 - 400 grams. Compounds are prepared at a volume of [1-2 mg/ml] in 1% methocellulose for oral dosing. Animals are separated into groups of five (5). Each assay includes a control group dosed with vehicle. Each group of animals is dosed with either vehicle or compound by oral gavage. Animals are allowed to rest for one, three, or six hours after dosing. Control animals are allowed to rest for three hours. At the appropriate times, the animals are anesthetized with Urethane at 1.5 g/kg, ip. Blood is drawn into a heparinized syringe via cardiac puncture.

Blood (0.5 ml) is aliquoted into separately-labeled 1.5 ml eppendorf tubes. Each sample is loaded with 5 µl of [15 mM] Arachidonic Acid, and placed in a 37 °C water bath for five minutes. After five minutes, the blood is stimulated with 5 µl of [5 mM] A23187 (Calcium Ionophore) and retained in the water bath for an additional 30 minutes. After the thirty minutes, the blood samples are removed from the water bath and centrifuged at 14,000 rpm for 2 minutes. Plasma is diluted to EIA buffer and an EIA is performed following manufacturer instructions (Cayman Chemical Co., Ann Arbor, MI, USA).

The results (Table 3) show the percent inhibition of 5-lipoxygenase by selected compounds at multiple time points post oral dosing. 50% inhibition or greater is considered significant.

Table 3

Cpd #	Dose	Time in hours	% inhibition
1	2 mg/kg	1 hour	62%
12	2 mg/kg	6 hours	80%
87	2mg/kg	1 hour	70%
87	2mg/kg	6 hours	94%
23	2 mg/kg	1 hour	80%
27	2 mg/kg	1 hour	88%
32	2 mg/kg	1 hour	88%
17	2 mg/kg	3 hours	70%
17	2 mg/kg	6 hours	94%
35	2mg/kg	1 hour	87%
35	2mg/kg	3 hours	97%
52	2 mg/kg	3 hours	61%
80	2 mg/kg	3 hours	73%
80	2 mg/kg	6 hours	88%
34	2 mg/kg	3 hours	38%

It can be seen from this Table that compounds of the present invention possess good activity with regard to their ability to inhibit the 5-lipoxygenase enzyme. Furthermore, several of the compounds administered at a single dose possess 5-lipoxygenase inhibitory activity of long duration. For example, **87** at a dose of 2 mg/kg, still inhibits 5-lipoxygenase activity by 94% at 6 hours post oral dosing.

These experiments also indicate that the compounds tested are orally bioavailable.

Example 12

Inhibition of 15-Lipoxygenase

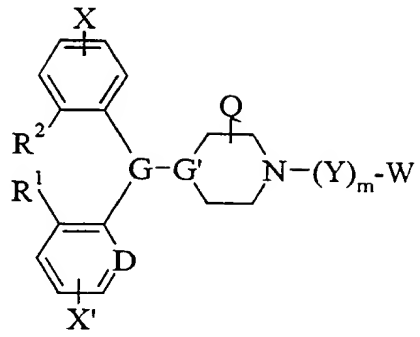
This assay examines the ability of a compound to inhibit production of 15-hydroxy-5, 8, 11, 13-eicosatetraenoic acid (15-HETE) via the action of 15-lipoxygenase on arachidonic acid.

15-lipoxygenase was purified from rabbit peritoneal polymorphonuclear leukocytes. The enzyme is responsible for the conversion of arachidonic acid (via oxygenation at carbon 15 of arachidonic acid) to 15-hydroperoxy-5, 8, 11, 13-eicosatetraenoic acid (15-HPETE), which then reduced to 15-hydroxy-5, 8, 11, 13-eicosatetraenoic acid (15-HETE).

The procedure for the assay is as follows. Arachidonic acid is co-incubated with 15-HETE for 5 min at 37°C in the presence or absence of different concentrations of test compound (10^{-8} to 10^{-5} M). Production of 15-HETE in each sample is then measured by radioimmunoassay. The 15-HETE levels produced in the vehicle control sample are then compared to those in which the test compound has been added. From this a percent inhibition of 15-HETE production by each concentration of test compound is calculated and the IC_{50} for inhibition of 15-HETE production for each test compound is determined. The IC_{50} s (nM) are 1300, 170, 46, 61, and 110 for compounds 1, 32, 35, 52 and 80, respectively.

We Claim:

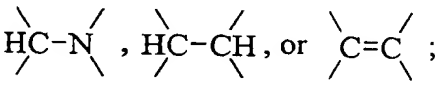
1. A compound of formula I:



I

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein:

X and X′ independently are hydrogen, halo, alkyl, alkenyl, alkynyl, alkoxy, trifluoromethyl or $-(Y')_{m'}-W'$;

G and G′ together form  ;

D is –CH= or =N-;

R^1 and R^2 independently are hydrogen or together are $-(CH_2)_n-$ in which n is equal to 0, 1, 2, or 3;

m and m'are independently 0 or 1;

Y and Y' are $-L^1-$ or $-L^2-V(Z)_t-L^3-$ in which t is 0 or 1;

L^1 is alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q)-, or $-N(R^3)-$;

L^2 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′)-, or $-N(R^4)-$, or (b) $-L^4-C(O)-N(Q')-$ or $-L^4(Q')-$, or (c) a direct bond;

L^3 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′′)-, or $-N(R^5)-$, or (b) a direct bond;

L^4 is (a) alkylene; alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′′)-, or $-N(R^5)-$, or (b) a direct bond;

V is (a) a divalent arene, a divalent heteroarene, or a divalent saturated heterocycle when t is 0, or (b) a trivalent arene or trivalent heteroarene when t is 1;

Q, Q′, and Q′′ independently are hydrogen, -AC(O)OR^6, or -AC(O)NR^{6}R^7;

W and W′ independently are -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, -N(OM)C(O)R^8, -C(O)NR^{8}R^9, or –C(O)OR^8, provided that at least one of W and W′ is –N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, or -N(OM)C(O)R^8.

Z is –A′′N(OM′)C(O)N(R^{10})R^{11}, -A′′N(R^{10})C(O)N(OM′)R^{11}, -A′′N(OM′)C(O)R^{11}, -A′C(O)N(OM′)R^{11}, -A′C(O)NR^{10}R^{11}, -A′C(O)OR^{10}, halo, CH_3, NR^{3}R^4, NR^{3}C(O)R^4, NO_2, CN, CF_3, S(O)$_2$NR^{3}R^4, S(O)$_2$R^3, SR^3, or S(O)R^3.

A, A′ and A′′ independently are a direct bond, alkylene, alkenylene, alkynylene, yloalkylaryl, yloarylalkyl, or diyloalkylarene or one of the foregoing in which one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and/or one or more methylidenes are replaced by =N-;

M and M′ independently are hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable group; and

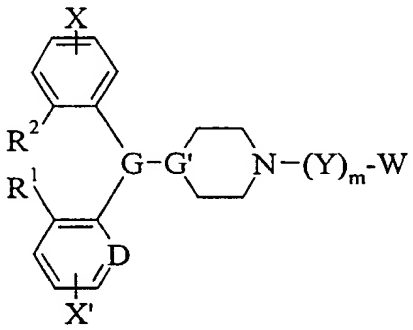
R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkylarylalkyl, or one of the foregoing in which one or more methylenes are replaced by -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and/or one or more methylidenes are replaced by =N-;

provided that, other than the oxygens bound to the sulfurs in -S(O)- and -S(O)$_2$-, when one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and when one or more methylidenes are replaced with =N-, such replacement does not result in two heteroatoms being covalently bound to each other;

and further provided that when m is 0, W is not -C(O)NR^{8}R^9, or –C(O)OR^8,

and further provided that in the substituent –AC(O)OOR^6, R^6 cannot be hydrogen when A is a direct bond.

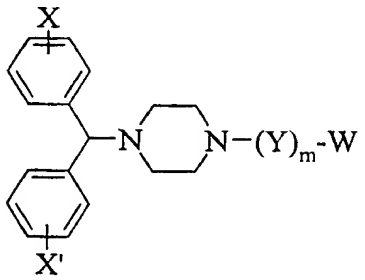
2. The compound of claim 1 having the formula I′′:



I

wherein the substituents are as defined in claim 1, and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

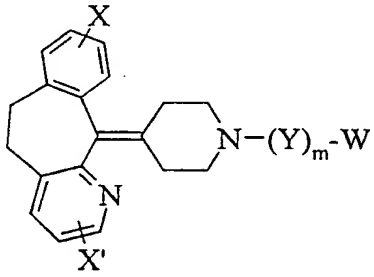
3. The compound according to claim 1 having the formula **II**:



II

wherein the substituents are as defined in claim 1, and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

4. The compound according to claim 1 having the formula **III**:



III

wherein the substituents are as defined in claim 1, and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

5. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1 and W is $-N(OH)C(O)NH_2$.

6. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^1-$, wherein L^1 is alkynylene, yloalkoxy, or yloalkoxyalkyl.

7. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 0, V is 1,4-phenylene or 1,3-phenylene, L^2 is yloalkoxy, and L^3 is alkylene, alkenylene, or alkynylene.

8. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 0, V is 2,5-furylene, L^2 is alkylene, and L^3 is alkylene, alkenylene, or alkynylene.

9. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 1, L^2 is yloalkoxy, V is trivalent heteroarene, Z is $-A'C(O)NR^{10}R^{11}$ or $-A'C(O)OR^{10}$, and W is $-N(OH)C(O)NH_2$.

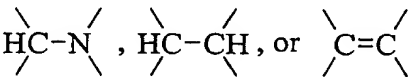
10. The compound according to either of claims 3 or 4 wherein X and X' are F, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 0, V is 1,4-phenylene or 1,3-phenylene, L^2 is yloalkoxy, and L^3 is alkylene, alkenylene, or alkynylene;

11. A compound selected from the group consisting of compounds **1**, **5**, **11**, **12**, **13**, **17**, **23**, **24**, **31**, **32**, **33**, **34**, **35**, **36**, **37**, **40**, **41**, **42**, **43**, **44**, **45**, **46**, **48**, **49**, **50**, **52**, **53**, **54**, **55**, **56**, **57**, **58**, **59**, **61**, **62**, **63**, **64**, **65**, **66**, **67**, **68**, **69**, **70**, **71**, **72**, **73**, **74**, **75**, **76**, **77**, **78**, **79**, **80**, **82**, **83**, **84**, **85**, **86**, **87**, **88**, **89**, **90**, **91**, **92**, **93**, and **94**.

12. A compound selected from the group consisting of compounds **17**, **32**, **34**, **35**, **46**, **52** and **80**.

13. A compound according to claim 1 wherein

X and X′ independently are hydrogen, halo or $-(Y')_{m'}-W'$;

G and G′ together form  ;

D is –CH= or =N-;

R^1 and R^2 independently are hydrogen or together are $-(CH_2)_2-$;

m and m'are independently 0 or 1;

Y and Y' are $-L^1-$ or $-L^2-V(Z)_t-L^3-$ in which t is 0 or 1;

L^1 is alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-;

L^2 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by –O- or -N(Q′)- or (b) $-L^4-C(O)-N(Q')-$;

L^3 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by –O- or -N(Q′′)-;

L^4 is alkylene;

V is (a) a divalent arene, a divalent heteroarene, or a divalent saturated heterocycle when t is 0, or (b) a trivalent arene or trivalent heteroarene when t is 1;

Q is hydrogen;

Q′, and Q′′ independently are $-AC(O)OR^6$, or $-AC(O)NR^6R^7$;

W and W′ independently are -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, -N(OM)C(O)R^8, -C(O)NR^8R^9, or –C(O)OR^8, provided that at least one of W and W′ is –N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, or -N(OM)C(O)R^8.

Z is -A′C(O)N$R^{10}R^{11}$, -A′C(O)OR^{10}, halo, NR^3C(O)R^4, NO_2, CN or CF_3;

A and A′ independently are a direct bond, alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced with –O-;

M and M′ independently are hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable group; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11}, if present, are independently hydrogen or alkyl in which one or more methylenes may be replaced by –O-;

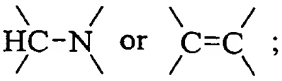
provided that, other than the oxygens bound to the sulfurs in -S(O)- and -$S(O)_2$-, when one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -$S(O)_2$- and when one or more methylidenes are replaced with =N-, such replacement does not result in two heteroatoms being covalently bound to each other;

and further provided that when m is 0, W is not -C(O)NR^8R^9, or –C(O)OR^8,

and further provided that in the substituent –AC(O)OOR^6, R^6 cannot be hydrogen when A is a direct bond.

14. A compound according to claim 13 wherein

X and X' independently are –H or halo;

G and G′ together form  ;

Y is –L^2-V$(Z)_t$-L^3- in which t is 0 or 1;

L^2 is C_1 to C_6 alkylene in which one or more methylenes may be replaced by –O-

V$(Z)_t$ is phenylene optionally substituted by -A′C(O)N$R^{10}R^{11}$, -A′C(O)OR^{10}, halo, NR^3C(O)R^4, NO_2, CN or CF_3 or furylene or oxolanylene;

L^3 is C_1 to C_6 alkylene in which one or more methylenes may be replaced by –O- or C_2 to C_6 alkynylene;

W is -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9 or -N(OM)C(O)R^8

A′ is methylene , vinylene or a direct bond.

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11}, if present, are independently hydrogen or C_1 to C_6 alkyl in which one or more methylenes may be replaced by –O-.

15. A compound according to claim 14 wherein

X is fluorine or chlorine;

X' is hydrogen or fluorine;

Y is –L^2-V$(Z)_t$-L^3- in which t is 0 or 1;

L^2 is C_1 to C_6 alkylene in which one methylene may be replaced by –O-

$V(Z)_t$ is phenylene optionally substituted by -A´C(O)$NR^{10}R^{11}$, -A´C(O)OR^{10}, halo, $NR^3C(O)R^4$, NO_2, CN or CF_3 or furylene or oxolanylene;

L^3 is C_1 to C_6 alkylene in which one methylene may be replaced by –O- or C_2 to C_6 alkynylene;

W is -N(OH)C(O)NH_2;

A´ is methylene , vinylene or a direct bond

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11}, if present, are independently hydrogen or C_1 to C_6 alkyl in which one methylene may be replaced by –O-.

16. A compound according to claim 1 wherein

X and X´ independently are hydrogen, halo, alkyl, alkenyl, alkynyl, alkoxy or trifluoromethyl;

W is -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9 or -N(OM)C(O)R^8;

17. A compound according to claim 1 wherein

L^4 is alkylene

Z is –N(OM´)C(O)N(R^{10})R^{11}, -N(R^{10})C(O)N(OM´)R^{11}, -N(OM´)C(O)R^{11}, -A´C(O)N(OM´)R^{11}, -A´C(O)$NR^{10}R^{11}$ or -A´C(O)OR^{10}.

18. A compound according to claim 1 wherein

X and X´ independently are -H, halo, alkyl, alkenyl, alkynyl, alkoxy or trifluoromethyl;

L^4 is alkylene

W is -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9 or -N(OM)C(O)R^8;

Z is –N(OM´)C(O)N(R^{10})R^{11}, -N(R^{10})C(O)N(OM´)R^{11}, -N(OM´)C(O)R^{11}, -A´C(O)N(OM´)R^{11}, -A´C(O)$NR^{10}R^{11}$ or -A´C(O)OR^{10}.

19. A compound according to claim 1 wherein when M or M´ is a metabolically cleavable group this is selected from an organic or inorganic anion, a pharmaceutically acceptable cation, acyl, alkyl, phosphate, sulfate and sulfonate, $NH_2C(O)$- or (alkyl)OC(O)-.

20. A compound according to claim 19 wherein acyl is (alkyl)C(O), including acetyl, propionyl and butyryl.

21. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any one of claims 1-20.

22. A method of simultaneously inhibiting both leukotriene- and histamine- mediated biological processes, the method comprising administering an effective leukotriene- and histamine- inhibiting amount of a compound according to any one of claims 1-20 to a subject in need of such inhibition.

23. A method of treating asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media, the method comprising administering to a patient suffering from asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media, an amount of a compound according to any one of claims 1-20 sufficient to reduce or eliminate the asthma.

24. A method according to claim 23 wherein the disease to be treated is selected from asthma and seasonal and perennial rhinitis.

Fig. 1

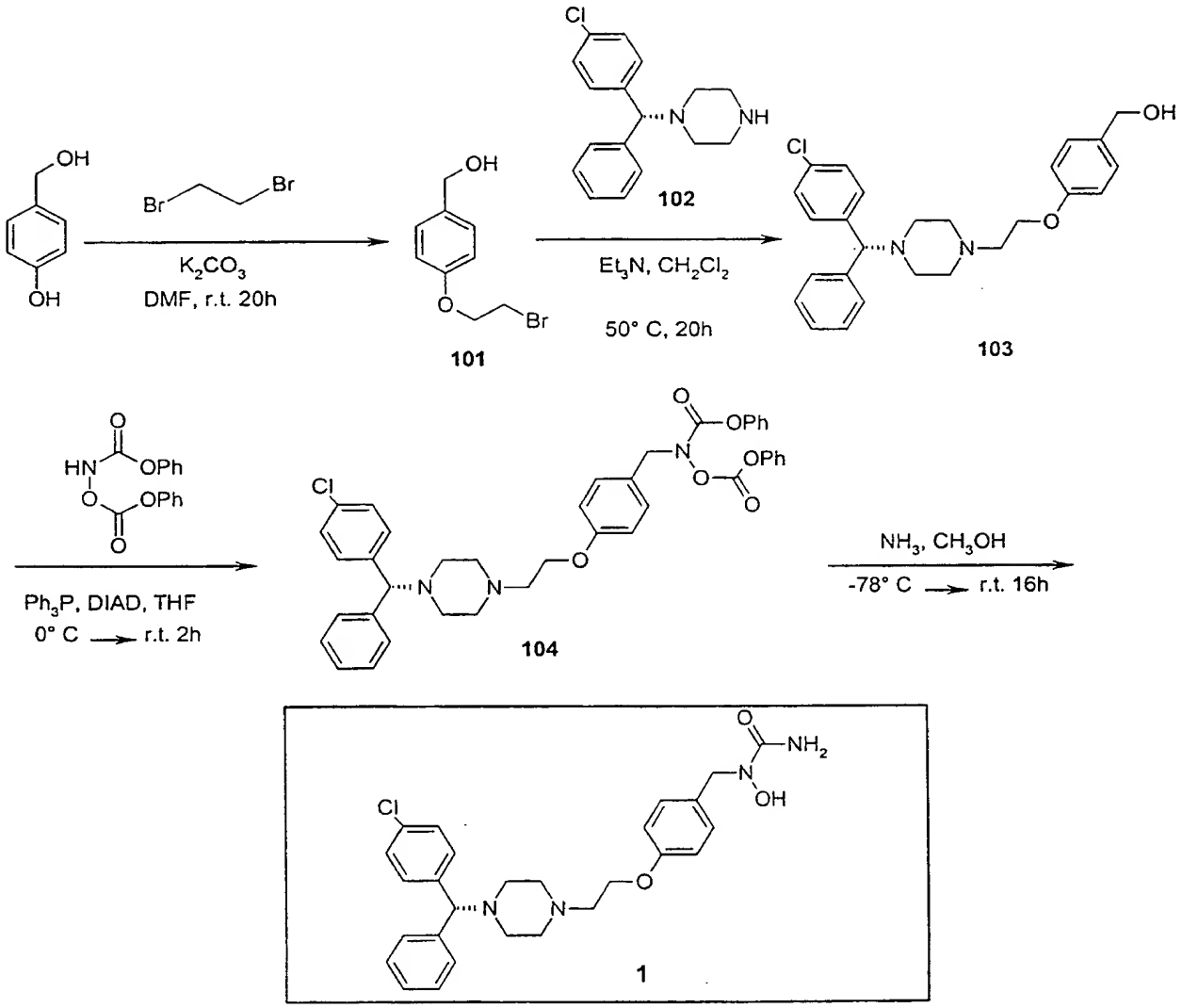

OH
Br
Br
K_2CO_3
DMF, r.t. 20h
OH
O
Br
101
Cl
NH
102
Et_3N, CH_2Cl_2
50° C, 20h
Cl
OH
O
103
HN
OPh
O
OPh
O
Ph_3P, DIAD, THF
0° C → r.t. 2h
Cl
OPh
N
OPh
O
O
104
NH_3, CH_3OH
-78° C → r.t. 16h
NH_2
N
OH
Cl
1

Fig. 2

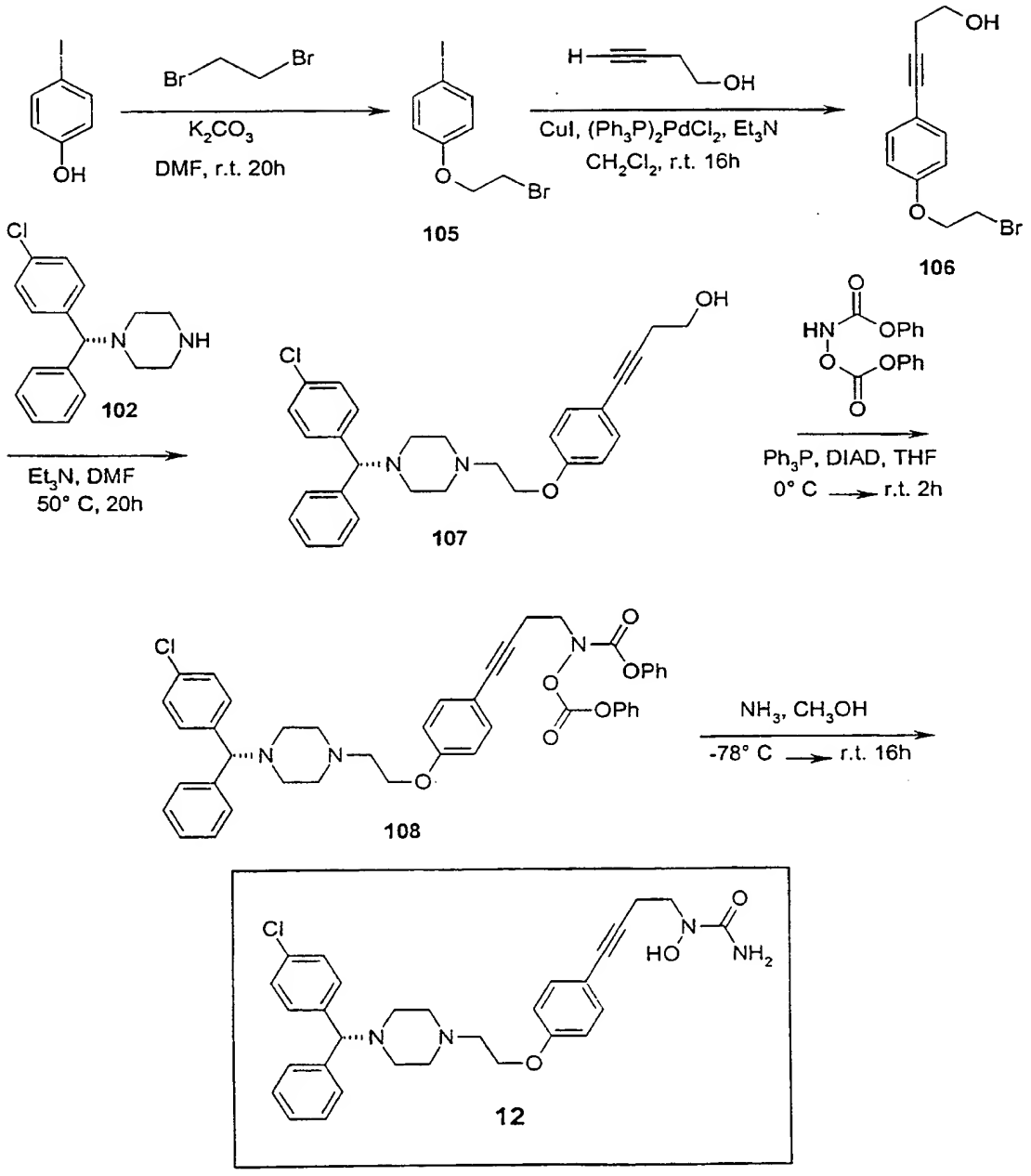

Br
Br
K_2CO_3
DMF, r.t. 20h
105
H
OH
CuI, $(Ph_3P)_2PdCl_2$, Et_3N
CH_2Cl_2, r.t. 16h
OH
Br
106
Cl
NH
102
Et_3N, DMF
50° C, 20h
OH
Cl
107
HN
OPh
O
OPh
Ph_3P, DIAD, THF
0° C → r.t. 2h
Cl
OPh
OPh
NH_3, CH_3OH
-78° C → r.t. 16h
108
Cl
HO
NH_2
12

Fig. 3

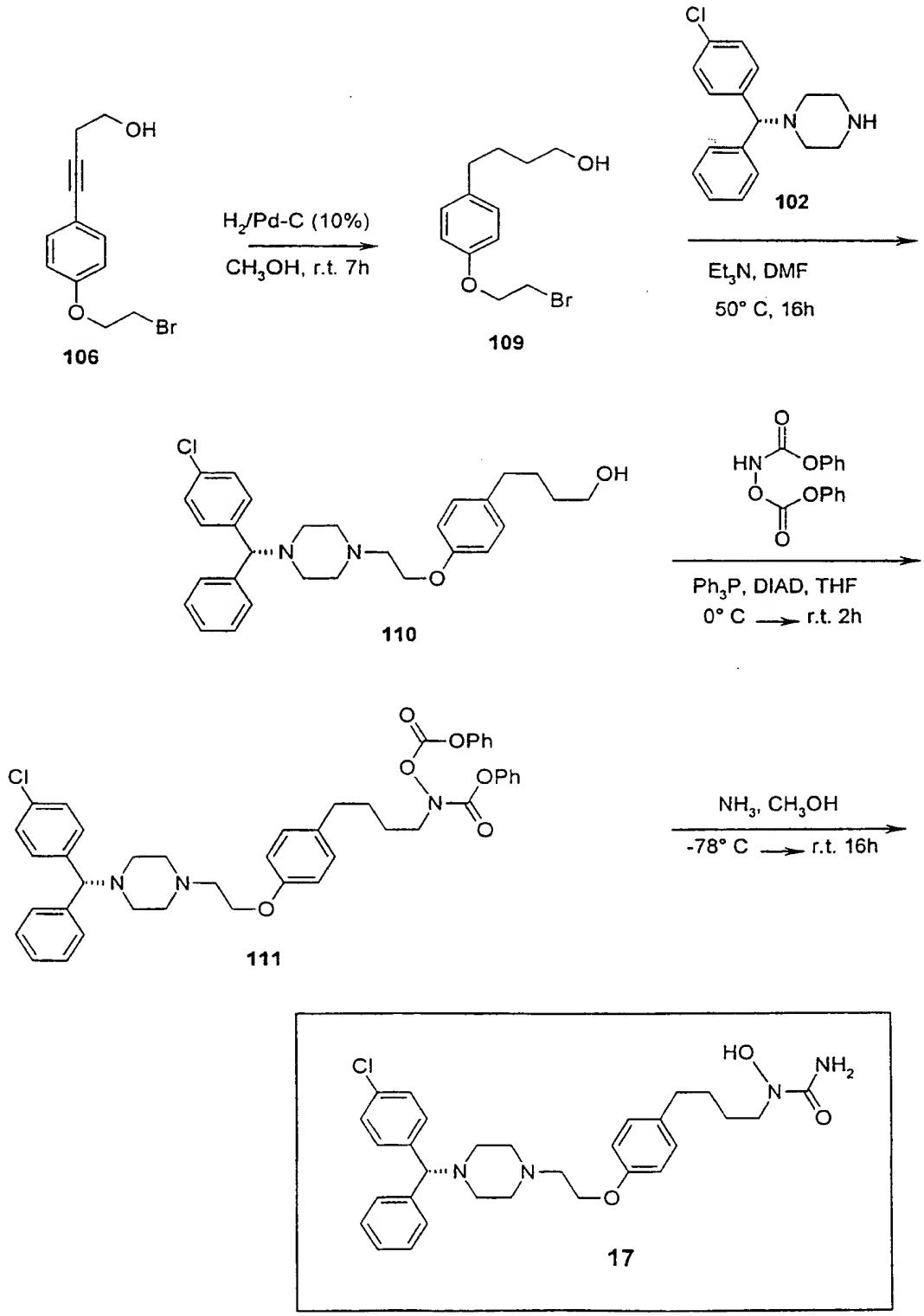
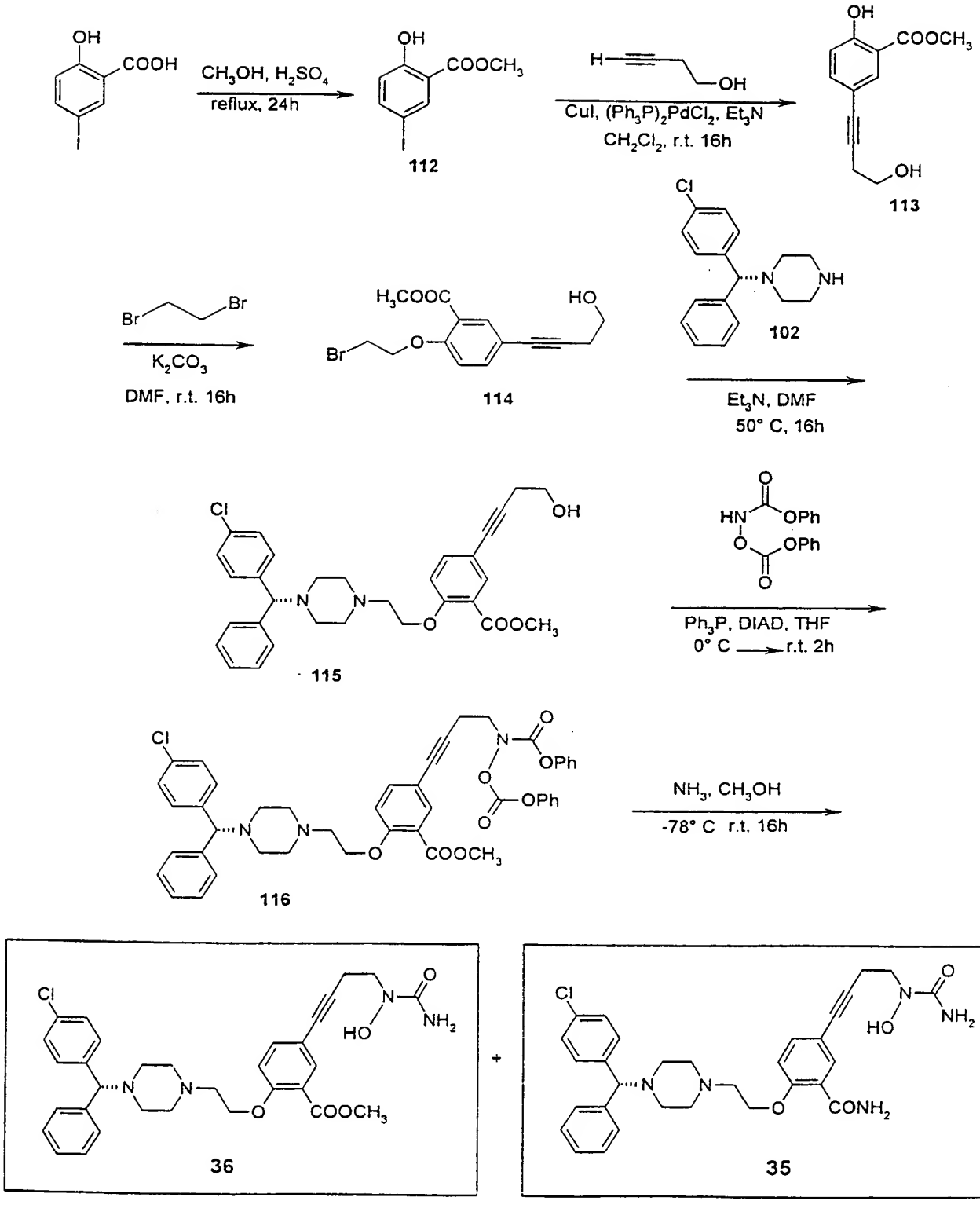

OH
Br
106
H_2/Pd-C (10%)
CH_3OH, r.t. 7h
OH
Br
109
Cl
N
NH
102
Et_3N, DMF
50° C, 16h
Cl
OH
110
HN
OPh
O
OPh
Ph_3P, DIAD, THF
0° C → r.t. 2h
Cl
OPh
OPh
111
NH_3, CH_3OH
-78° C → r.t. 16h
Cl
HO
NH_2
17

Fig. 4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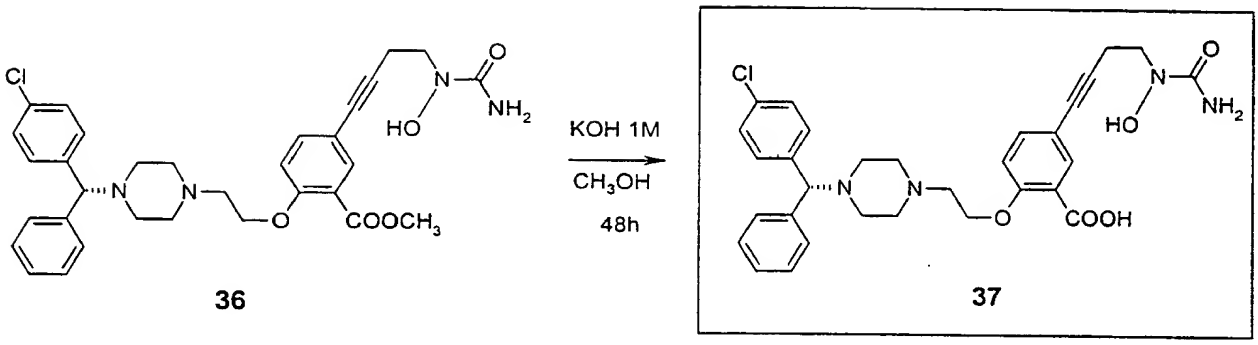
COOH
CH_3OH, H_2SO_4
reflux, 24h
OH
$COOCH_3$
112
H
OH
CuI, $(Ph_3P)_2PdCl_2$, Et_3N
CH_2Cl_2, r.t. 16h
OH
$COOCH_3$
OH
113
Cl
N
NH
102
Br
Br
K_2CO_3
DMF, r.t. 16h
H_3COOC
HO
Br
O
114
Et_3N, DMF
50° C, 16h
Cl
OH
N
N
O
$COOCH_3$
115
HN
OPh
O
OPh
O
Ph_3P, DIAD, THF
0° C → r.t. 2h
Cl
N
OPh
O
OPh
O
N
N
O
$COOCH_3$
116
NH_3, CH_3OH
-78° C r.t. 16h
Cl
N
HO
NH_2
N
N
O
$COOCH_3$
36
+
Cl
N
HO
NH_2
N
N
O
$CONH_2$
35

Fig. 5



36 37

Fig. 6

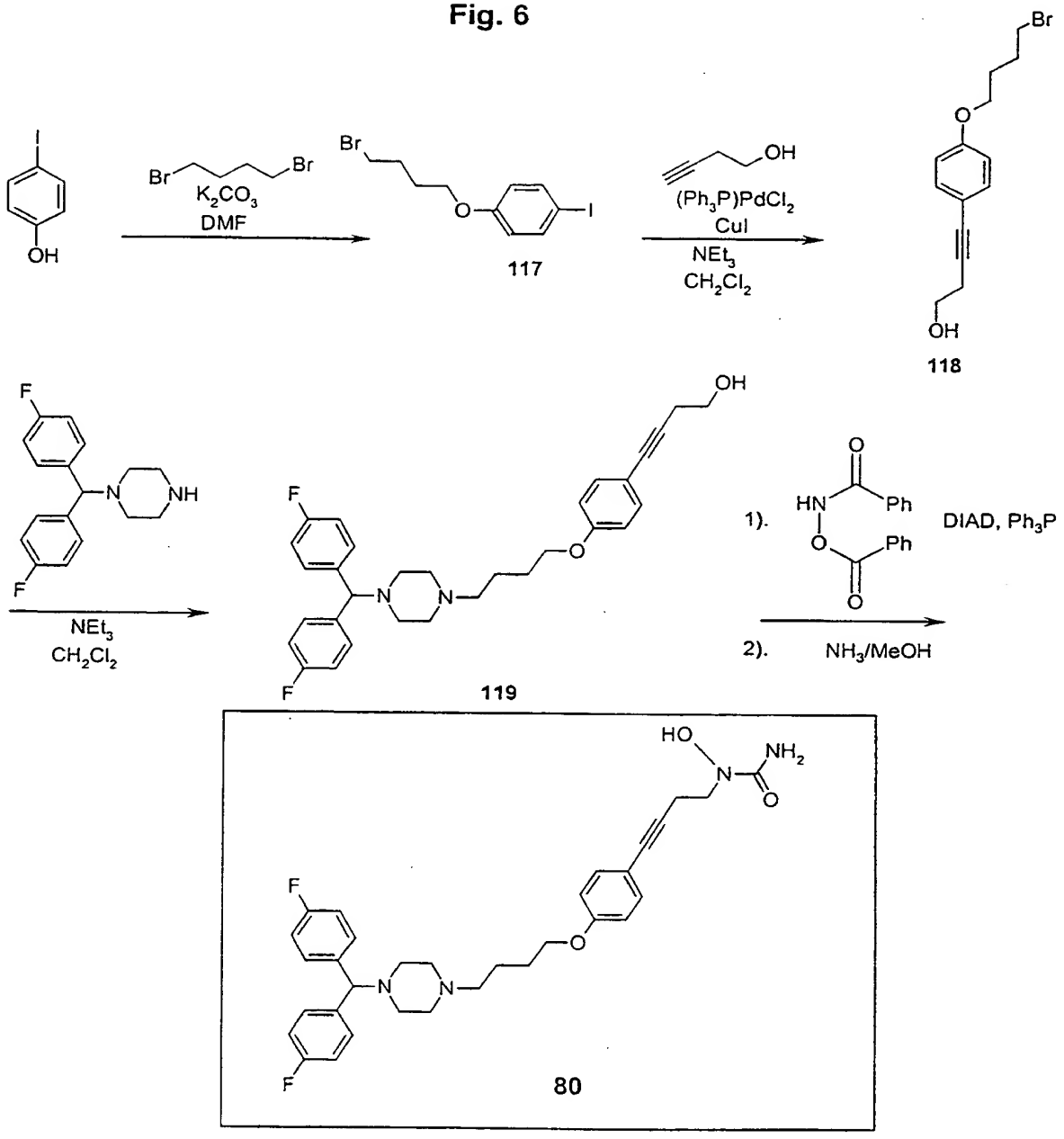

Br
OH
K2CO3
DMF
117
(Ph3P)PdCl2
CuI
NEt3
CH2Cl2
118
NH
NEt3
CH2Cl2
119
1).
DIAD, Ph3P
2).
NH3/MeOH
HO
NH2
80

Fig. 7

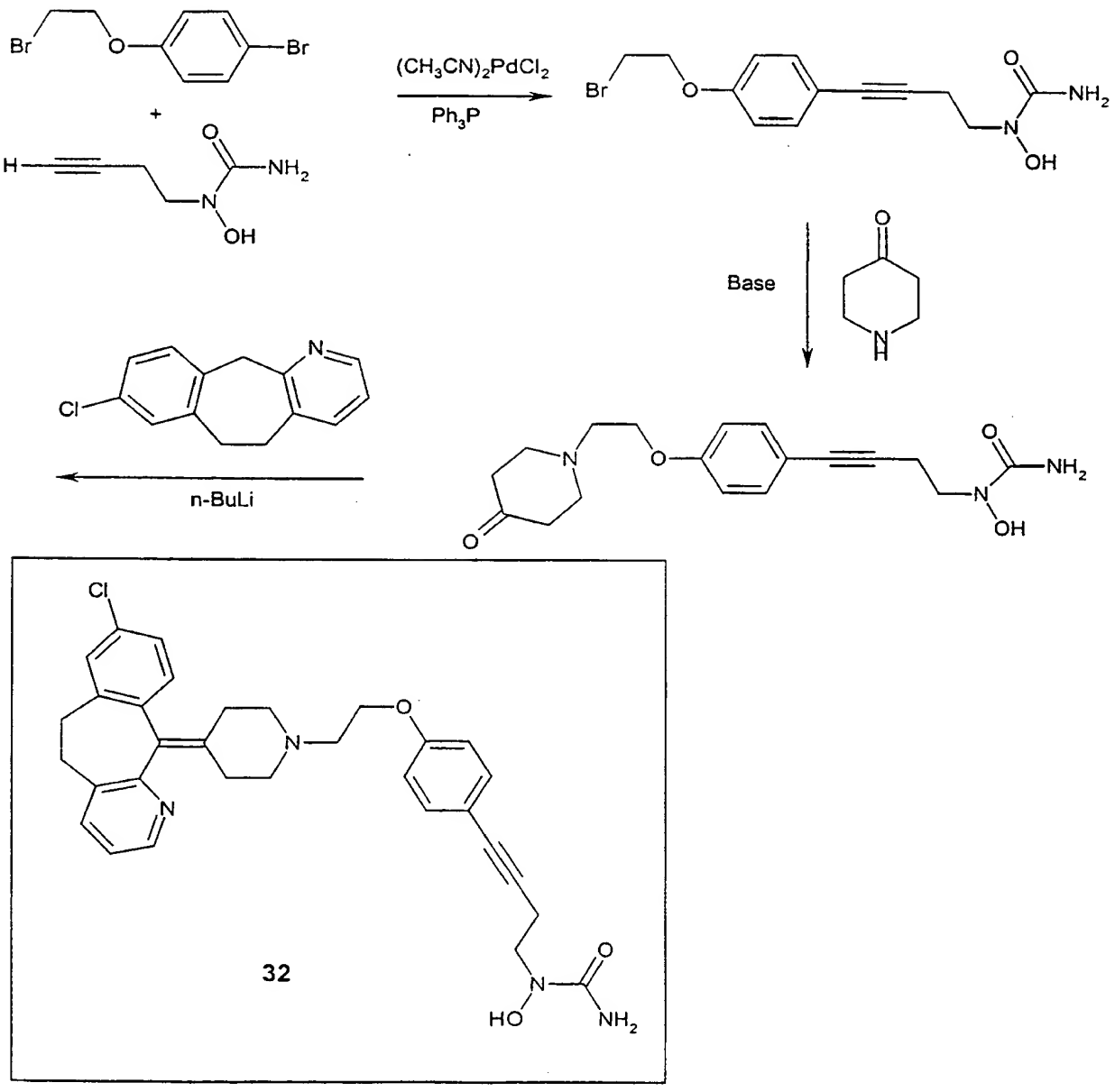


Fig. 8

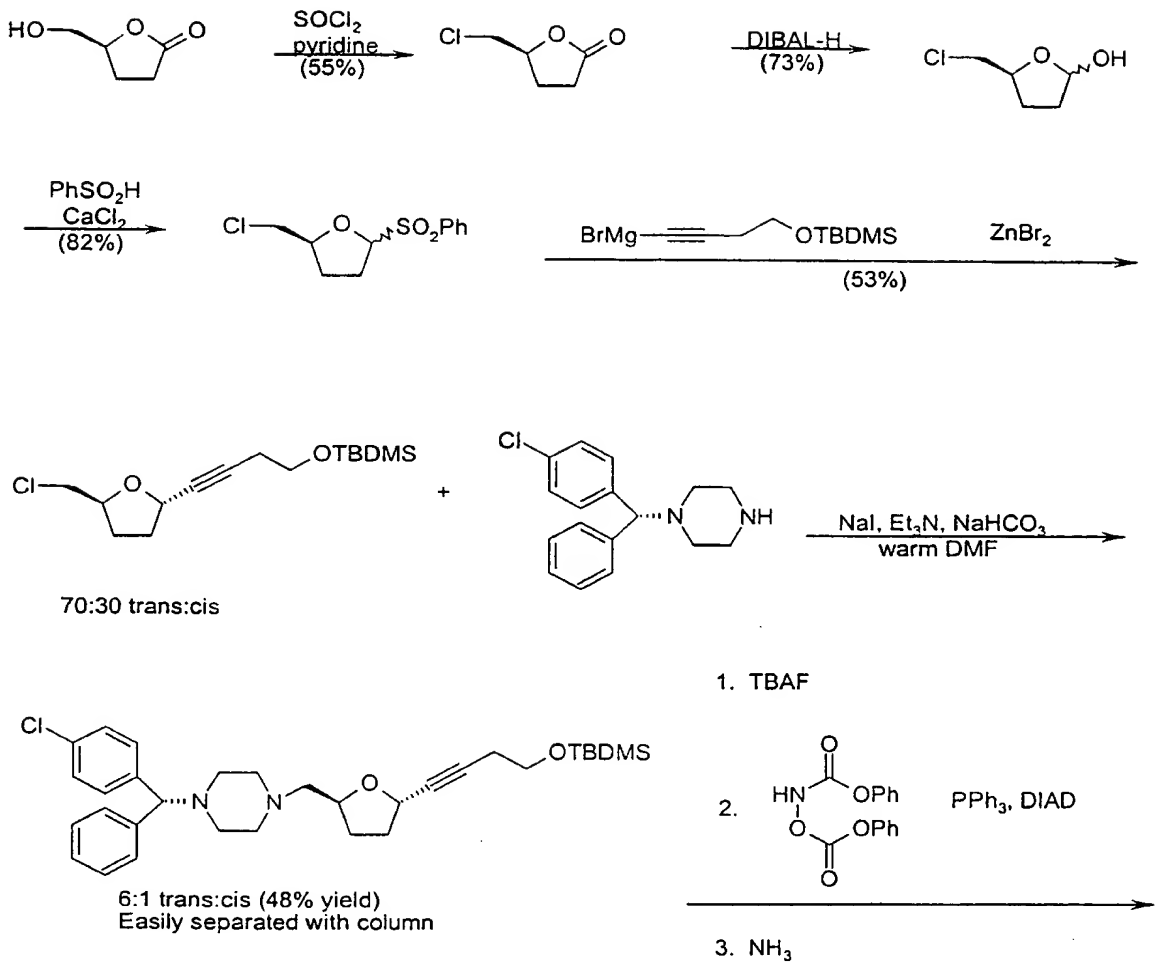
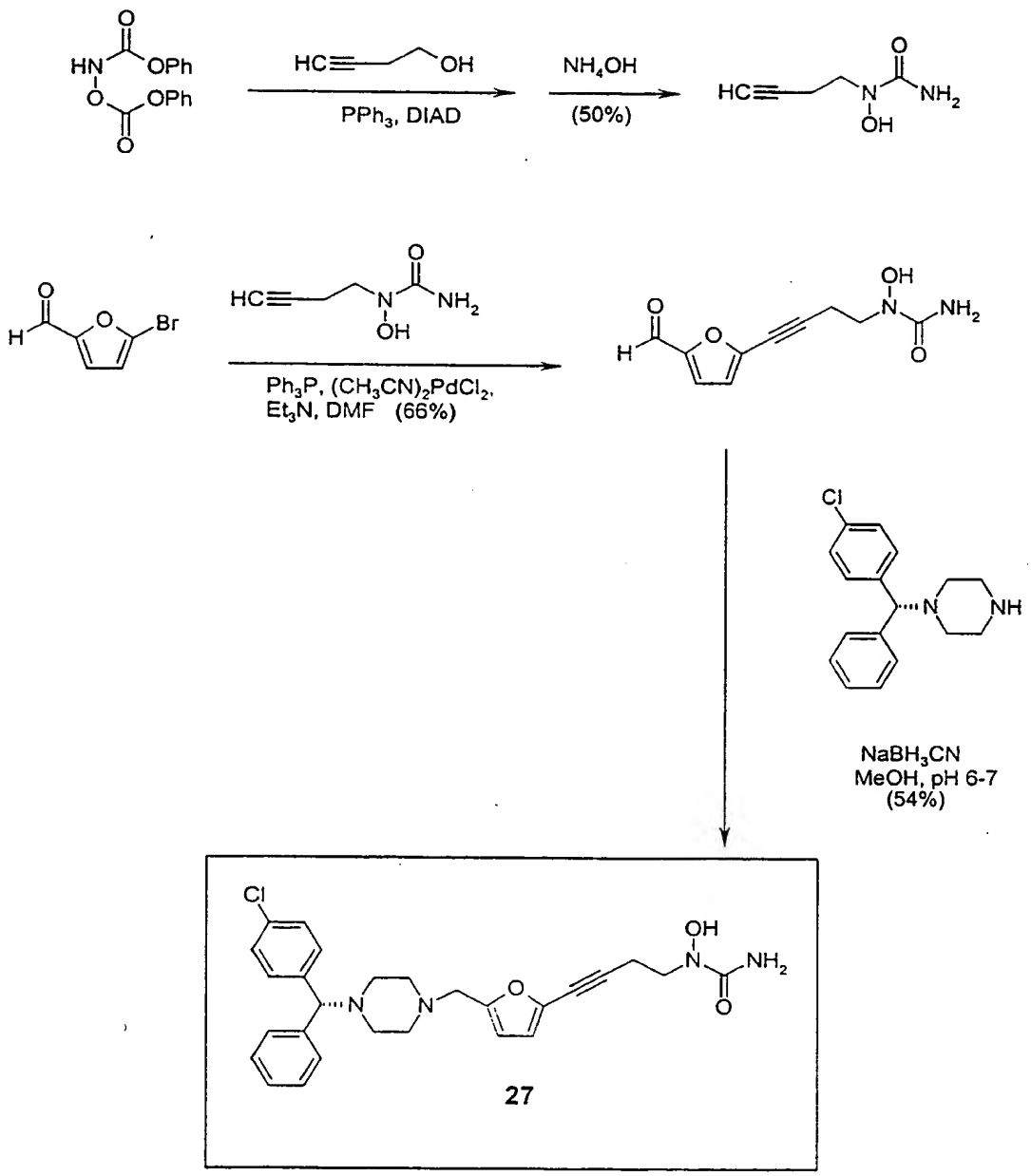

HO
O
O
SOCl2
pyridine
(55%)
Cl
O
O
DIBAL-H
(73%)
Cl
O
OH
PhSO2H
CaCl2
(82%)
Cl
O
SO2Ph
BrMg
OTBDMS
ZnBr2
(53%)
Cl
O
OTBDMS
70:30 trans:cis
+
Cl
N
NH
NaI, Et3N, NaHCO3
warm DMF
1. TBAF
Cl
N
N
O
OTBDMS
6:1 trans:cis (48% yield)
Easily separated with column
2.
HN
O
OPh
OPh
O
PPh3, DIAD
3. NH3
Cl
N
N
O
OH
N
NH2
O
46

Fig. 9


HC≡ OH
PPh3, DIAD
NH4OH
(50%)
Br
Ph3P, (CH3CN)2PdCl2,
Et3N, DMF (66%)
Cl
NaBH3CN
MeOH, pH 6-7
(54%)
27

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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

COMPOUNDS AND METHODS FOR TREATMENT OF ASTHMA, ALLERGY AND INFLAMMATORY DISORDERS

BACKGROUND OF THE INVENTION

Field Of The Invention

The invention relates to the field of 1,4 substituted piperazines, 1,4 substituted piperidines, and 1-substituted, 4-alkylidenyl piperidines.

Summary of the Related Art

Leukotrienes are potent local mediators, playing a major role in inflammatory and allergic responses including arthritis, asthma, psoriasis, and thrombotic disease. Leukotrienes are straight chain eicosanoids produced by the oxidation of arachidonic acid by lipoxygenases. Arachidonic acid is oxidized by 5-lipoxygenase and ultimately converted to leukotrienes A4, B4, C4 , D4 or E4. 15-Lipoxygenase is responsible for the conversion of arachidonic acid to various biologically active metabolites including 15-hydroxy-5,8,11,13-eicosatetraenoic acid (15-HETE). Both of these mediators have been implicated in the pathogenesis of airway and allergic diseases such as asthma by contributing to bronchoconstriction, mucus secretion, and eosinophil migration. A mixture of one or more of such leukotrienes are known to be potent bronchoconstrictors. Thus, leukotrienes have been shown to play an important role in the pathology of asthma. Rigorous proof for the role of leukotrienes in asthma has been provided by several pivotal clinical trials in which orally administered 5-lipoxygenase (5-LO) inhibitors (or LTD4 receptor antagonists) produce clear therapeutic benefit in asthma patients. These benefits include reduction in the use of classic asthma therapies such as beta agonists and corticosteroids.

It is well known in the art that certain hydroxyurea- and hydroxyamide- substituted aromatic compounds can function as 5-LO inhibitors. For example, WO 92/09567 and WO 92/09566 disclose a wide variety of N-hydroxyurea and hydroxamic acid compounds as inhibitors of the lipoxygenase enzyme.

Histamine has been established to play a role in inflammation in general. Antihistamines are well established most notably for allergy control. Furthermore, histamine is believed to play a role in asthma. For example, histamine and cysteinyl leukotrienes (cLT's) are both known to be key mediators in airway tone. Clinical studies have shown that a combination therapy of a cLT receptor antagonist and an antihistamine administered to twelve asthma patients, reduced early asthmatic responses (EAR) and late asthmatic responses (LAR) to a greater extent than either single-acting agent alone (A. Roquet, et al., *Am. J. Respir Crit. Care Med*, **155**, 1856 (1997)). This indicates that histamine plays a role in asthma.

It is well known that certain [bis(substituted and/or unsubstituted aryl) methyl- and methylene]-1-piperidyl compounds possess antihistaminergic activity, and numerous publications disclose such. For example, Yanni *et al.* (US 4,810,713 and 4,950,674) disclose [[bis(aryl)methyl- or methylene-]-1-piperidinyl]alkoxy -aryl and -heteroaryl compounds for the

treatment of allergic phenomena, including asthma and rhinitis. Teng *et al.* (US 5,070,087) disclose [bis(aryl)methyl- and methylene]-N-[(phenoxy and phenylthio)alkyl]piperidines for countering effects of histamine in allergies.

Others have shown [bis(aryl)methyl]piperazin-1-yl compounds for use as antiasthmatics and antiallergics that inhibit leukotriene release (*e.g.*, JP 97077754). U.S. 4,525,358 teaches 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid and its amides as antiallergic, spasmolytic, and antihistamine agents. JP 7138230 discloses 4-aralkyl-1-piperazinyl-unsaturated carboxylic acid derivatives useful an antiallergic agents for the treatment of, for example, asthma and rhinitis. WO 97/23466 describes the preparation of N-diarylmethylpiperazines as analgesics.

None of the art, however, teaches, suggests, or contemplates combining the 5-LO and 15-LO inhibiting functionality of hydroxyurea moieties with the antihistaminergic properties of [bis(substituted and/or unsubstituted aryl) methyl- and methylene]-1-piperidyl or –1-piperazinyl moieties in a single entity to yield a compound possessing the dual functions as an antihistaminergic and a 5-LO/15-LO inhibitor.

SUMMARY OF THE INVENTION

The present invention provides novel compounds having dual properties, each compound possessing both lipoxygenase inhibition properties as well as antihistaminergic properties. In a preferred embodiment, each of the novel compounds of the invention functions as both a 5-LO and/or 15-LO inhibitor as well as a histamine H1 receptor antagonist.

The compounds of the invention are useful for treating conditions in which there is likely to be a histamine and/or leukotriene component. These conditions include preferably asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media. Accordingly, the invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of treating asthma and rhinitis with the pharmaceutical compositions.

The compounds disclosed herein can also be used as research tools to study biological pathways involving both leukotrienes and histamine and, in particular, further elucidate the role histamine plays in bronchoconstriction.

All patent applications, patents, and other publications recited herein are hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 displays the synthesis of compound **1**.

Figure 2 displays the synthesis of compound **12**.

Figure 3 displays the synthesis of compound **17**.

Figure 4 displays the synthesis of compound **35** and **36**.

Figure 5 displays the synthesis of compound **37**.

Figure 6 displays the synthesis of compound **80**.

Figure 7 displays the synthesis of compound **32**.

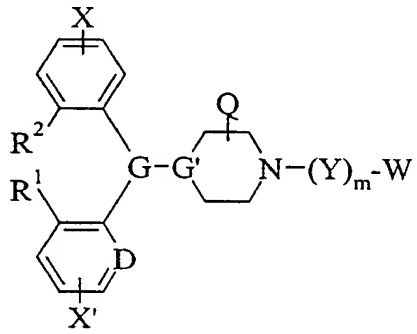
Figure 8 displays the synthesis of compound **46**.

Figure 9 displays the synthesis of compound **27**.

DETAILED DESCRIPTION OF THE INVENTION

The Compounds

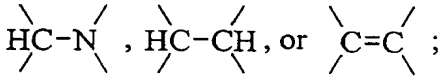
In one aspect, the present invention comprises compounds of formula I, including geometrical isomers, enantiomers, diastereomers, racemates, and pharmaceutically acceptable salts thereof:



I

wherein:

X and X′ independently are hydrogen, halo, alkyl, alkenyl, alkynyl, alkoxy, trifluoromethyl or $-(Y')_{m'}-W'$;

G and G′ together form  ;

D is –CH= or =N-;

R^1 and R^2 independently are hydrogen or together are $-(CH_2)_n-$ in which n is equal to 0, 1, 2, or 3;

m and m′ are independently 0 or 1;

Y and Y′ are $-L^1-$ or $-L^2-V(Z)_t-L^3-$ in which t is 0 or 1;

L^1 is alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q)-, or $-N(R^3)-$;

L^2 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′)-, or $-N(R^4)-$, or (b) $-L^4-C(O)-N(Q')-$ or $-L^4(Q')-$, or (c) a direct bond;

L^3 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′′)-, or $-N(R^5)-$, or (b) a direct bond;

L^4 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′′)-, or $-N(R^5)-$, or (b) a direct bond;

V is (a) a divalent arene, a divalent heteroarene, or a divalent saturated heterocycle when t is 0, or (b) a trivalent arene or trivalent heteroarene when t is 1;

Q, Q′, and Q′′ independently are hydrogen, -AC(O)OR^6, or -AC(O)NR^{6}R^7;

W and W′ independently are -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, -N(OM)C(O)R^8, -C(O)NR^{8}R^9, or –C(O)OR^8, provided that at least one of W and W′ is –N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, or -N(OM)C(O)R^8.

Z is –A′′N(OM′)C(O)N(R^{10})R^{11}, - A′′N(R^{10})C(O)N(OM′)R^{11}, - A′′N(OM′)C(O)R^{11}, -A′C(O)N(OM′)R^{11}, -A′C(O)NR^{10}R^{11}, -A′C(O)OR^{10}, halo, CH_3, NR^{3}R^4, NR^{3}C(O)R^4, NO_2, CN, CF_3, S(O)$_2$NR^{3}R^4, S(O)$_2$R^3, SR^3, or S(O)R^3.

A, A′ and A′′ independently are a direct bond, alkylene, alkenylene, alkynylene, yloalkylaryl, yloarylalkyl, or diyloalkylarene or one of the foregoing in which one or more methylenes are replaced by -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and/or one or more methylidenes are replaced by =N-;

M and M′ independently are hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable group; and

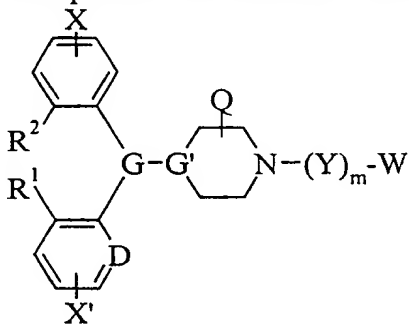
R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkylarylalkyl, or one of the foregoing in which one or more methylenes are replaced by -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and/or one or more methylidenes are replaced by =N-;

provided that, other than the oxygens bound to the sulfurs in -S(O)- and -S(O)$_2$-, when one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and when one or more methylidenes are replaced with =N-, such replacement does not result in two heteroatoms being covalently bound to each other;

and further provided that when m is 0, W is not -C(O)NR^{8}R^9, or –C(O)OR^8,

and further provided that in the substituent –AC(O)OR$_6$, R$_6$ cannot be hydrogen when A is a direct bond.

Preferably, compounds of the present invention are those having formula **I′**:



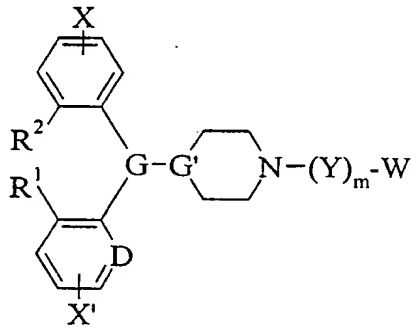
I′

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein each of the variables is as defined above, except that:

X and X′ independently are hydrogen, halo, alkyl, alkenyl, alkynyl, alkoxy, or trifluoromethyl; and

W is -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, or -N(OM)C(O)R^8.

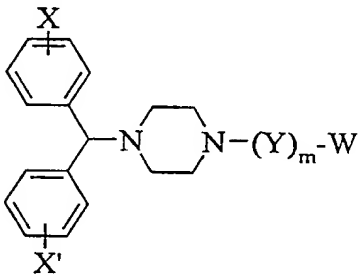
In another preferred embodiment, the compounds of the present invention are given by formula I′′:



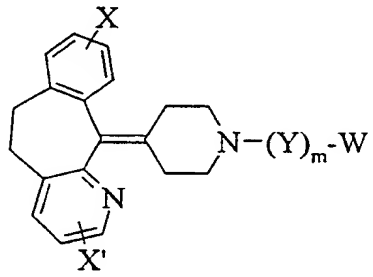
I′′

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein each of the variables is as defined above.

In other preferred embodiments, compounds of formula I are represented by the following formulas, II and III:



II



III

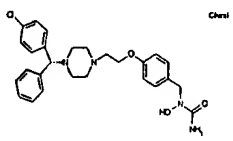
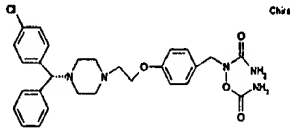
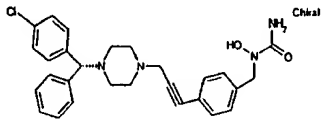
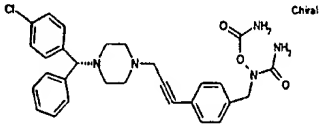
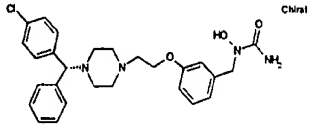
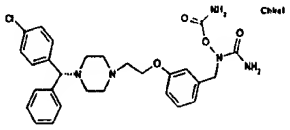
and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein each of the variables is as defined above.

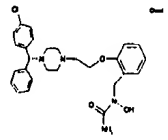
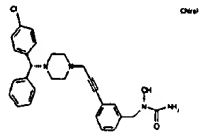
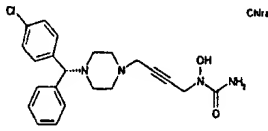
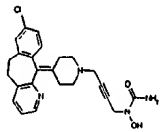
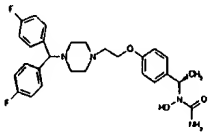
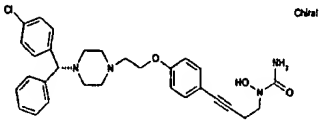
More preferred embodiments of the compounds of formula II and III and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, are those wherein each of the variables is as defined above except that:

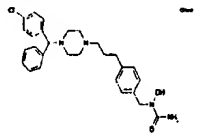
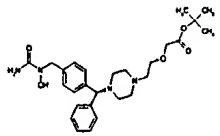
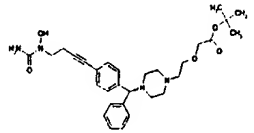
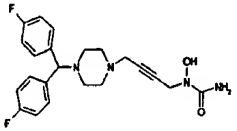
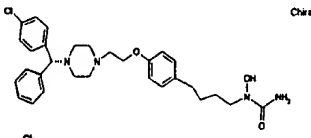
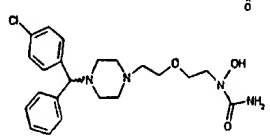
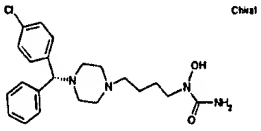
1. X is -Cl, X′ is hydrogen, m is 1 and W is -N(OH)C(O)NH_2;
2. X is -Cl, X′ is hydrogen, m is 1, Y is -L^1-, wherein L^1 is alkynylene, yloalkoxy, or yloalkoxyalkyl;
3. X is -Cl, X′ is hydrogen, m is 1, Y is -L^2-V(Z)$_t$ -L^3-, t is 0, V is 1,4-phenylene or 1,3-phenylene, L^2 is yloalkoxy, and L^3 is alkylene, alkenylene, or alkynylene;
4. X is -Cl, X′ is hydrogen, m is 1, Y is -L^2-V(Z)$_t$ -L^3-, t is 0, V is 2,5-furylene, L^2 is alkylene, and L^3 is alkylene, alkenylene, or alkynylene; or

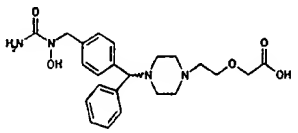
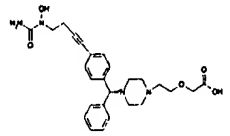
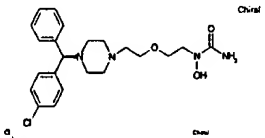
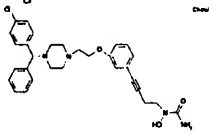
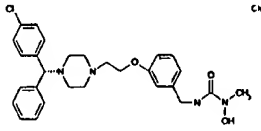
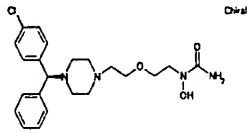
5. X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 1, L^2 is yloalkoxy, V is trivalent heteroarene, Z is $-A'C(O)NR^{10}R^{11}$ or $-A'C(O)OR^{10}$ and W is $-N(OH)C(O)NH_2$.
6. X and X' are F, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 0, V is 1,4-phenylene or 1,3-phenylene, L^2 is yloalkoxy, and L^3 is alkylene, alkenylene, or alkynylene;

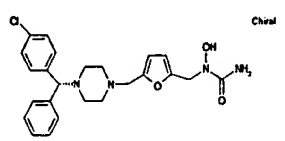
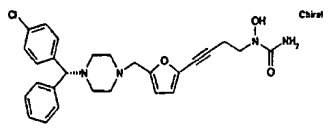
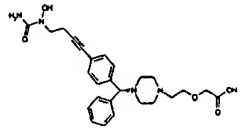
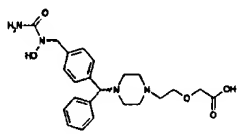
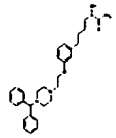
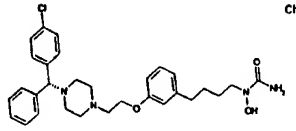
Compounds of the invention include those shown in TABLE I as follows:

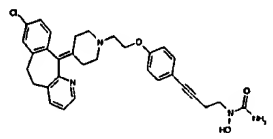
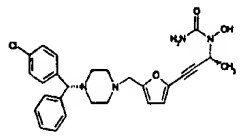
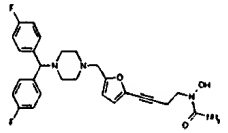
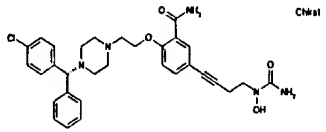
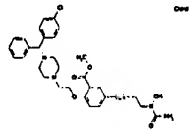
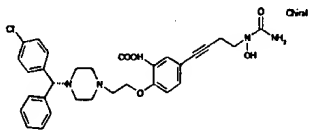
CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
1		CHIRAL R				3,07	N-{[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}amino-N-hydroxyamide
2		CHIRAL R				2,72	N-{[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}aminocarbonylamino aminooate
3		CHIRAL R				3,62	N-{[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}prop-1-ynyl)phenyl]methyl}amino-N-hydroxyamide
4		CHIRAL R				3,27	N-{[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}prop-1-ynyl)phenyl]methyl}aminocarbonylamino aminooate
5		CHIRAL R				3,18	N-{[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}amino-N-hydroxyamide
6		CHIRAL R				2,82	N-{[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}aminocarbonylamino aminooate

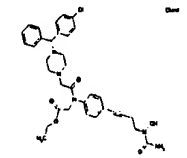
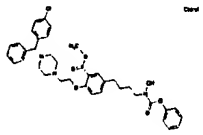
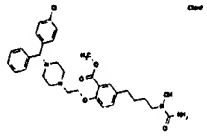
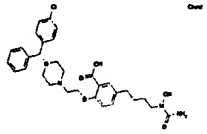
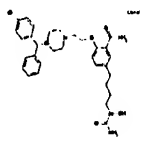
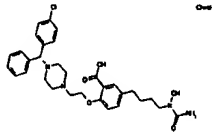
CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
7		CHIRAL R				3,08	N-{[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}amino-N-hydroxyamide
8		CHIRAL R				3,62	N-{[3-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}prop-1-ynyl)phenyl]methyl}amino-N-hydroxyamide
9		CHIRAL R				1,76	N-(4-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}but-2-ynyl)amino-N-hydroxyamide
10						3,65	amino-N-{4-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl]but-2-ynyl}-N-hydroxyamide
11		RACEMATE				3,18	amino-N-{[4-(2-{4-[bis(4-fluorophenyl)methyl]piperazinyl}ethoxy)phenyl]ethyl}-N-hydroxyamide
12		CHIRAL R			533,3	4,19	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]but-3-ynyl}amino-N-hydroxyamide

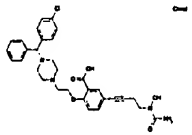
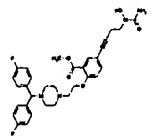
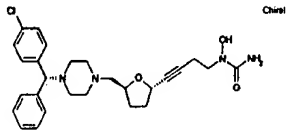
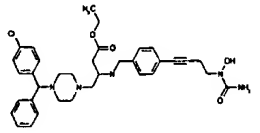
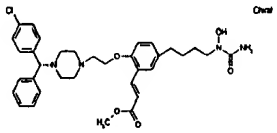
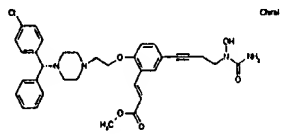
CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
13		CHIRAL R				3,98	N-{[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}propyl) phenyl]methyl}amino-N-hydroxyamide
14		RACEMATE				1,65	tert-butyl 2-{2-[4-({4-[(aminohydroxycarbonylamino)methyl]phenyl} phenylmethyl)piperazinyl]ethoxy}acetate
15		RACEMATE				2,77	tert-butyl 2-{2-[4-({4-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl}phenylmethyl)piperazinyl]ethoxy} acetate
16						1,33	amino-N-(4-{4-[bis(4-fluorophenyl)methyl]piperazinyl}but-2-ynyl)-N-hydroxyamide
17		CHIRAL R		148 - 150	536,64	4,55	N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]butyl}amino-N-hydroxyamide
18		RACEMATE				1,05	amino-N-[2-(2-{4-[(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)ethyl]-N-hydroxyamide
19		CHIRAL R				2,37	N-(4-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}butyl) amino-N-hydroxyamide

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
20		RACEMATE	2 HCl			-0,04	2-{2-[4-({4-[(aminohydroxycarbonylamino)methyl]phenyl} phenylmethyl)piperazinyl]ethoxy}acetic acid
21		RACEMATE	2 HCl			1,08	2-{2-[4-({4-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl}phenylmethyl)piperazinyl]ethoxy} acetic acid
22		CHIRAL R				1,34	N-[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)ethyl]amino-N-hydroxyamide
23		CHIRAL R			533,2	4,19	N-{4-[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]but-3-ynyl}amino-N-hydroxyamide
24		CHIRAL R			509,2	3,82	N-{[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}(methyl(hydroxyamino))carbox amide
25		CHIRAL S				1,34	N-[2-(2-{4-[(1S)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)ethyl]amino-N-hydroxyamide

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
26		CHIRAL R			455	2,44	N-{[5-({4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}methyl) (2-furyl)]methyl}amino-N-hydroxyamide
27		CHIRAL R			493,2	3,45	N-{4-[5-({4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}methyl) (2-furyl)]but-3-ynyl}amino-N-hydroxyamide
28		RACEMATE	2 TFA		480,2	1,08	2-{2-[4-({4-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl}phenylmethyl)piperazinyl]ethoxy} acetic acid
29		RACEMATE	2 TFA		442,2	-0,04	2-{2-[4-({4-[(aminohydroxycarbonylamino)methyl]phenyl} phenylmethyl)piperazinyl]ethoxy}acetic acid
30					503,4	3,93	amino-N-[4-(3-{2-[4-(diphenylmethyl)piperazinyl]ethoxy}phenyl) butyl]-N-hydroxyamide
31		CHIRAL R			537,1	4,64	N-{4-[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]butyl}amino-N-hydroxyamide

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
32					557,14	6,08	amino-N-[4-(4-{2-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene))piperidyl]ethoxy}phenyl)but-3-ynyl]-N-hydroxyamide
33		MIXTURE			493,2	3,48	N-{3-[5-({4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}methyl) (2-furyl)]-1-methylprop-2-ynyl}amino-N-hydroxyamide
34					494	3,03	amino-N-{4-[5-({4-[bis(4-fluorophenyl)methyl]piperazinyl}methyl)(2-furyl)]but-3-ynyl}- N-hydroxyamide
35		CHIRAL R		156 - 158	575,45	3,14	2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzamide
36		CHIRAL R			591,1	4,33	methyl 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonyl amino)but-1-ynyl]benzoate
37		CHIRAL R			577,1	3,89	2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzoic acid

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
38		CHIRAL R			616,1	3,64	ethyl 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}-N-{4-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl}acetylamino)acetate
39		CHIRAL R			672,1	7,37	methyl 2-(2-{4-[(R)-(4-chlorophenyl)(phenyl)methyl]-1-piperazinyl}ethoxy)-5-{4-[hydroxy(phenoxycarbonyl)amino]butyl} benzoate
40		CHIRAL R			595,2	4,83	methyl 2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzoate
41		CHIRAL R			581,2	4,39	2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzoic acid
42		CHIRAL R			580,2	3,64	2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl] benzamide
43		CHIRAL R	2 HCl		581,2	4,39	2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzoic acid

CPD #	STRUCTURE	STEREO CHEMISTRY	SALT	MELTING POINT	MS OBS MASS	LOGP	NAME
44		CHIRAL R	2 HCl		577	3,89	2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzoic acid
45					593,3	3,91	methyl 5-[4-(aminohydroxycarbonylamino)but-1-ynyl]-2-(2-{4-[bis(4-fluorophenyl)methyl]piperazinyl}ethoxy)benzoate
46		CHIRAL			497	2,75	N-{4-[5-({4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}methyl)(2S,5S)oxolan-2-yl]but-3-ynyl}amino-N-hydroxyamide
47		MIXTURE			633	4,8	ethyl 3-[({4-[4-(aminohydroxycarbonylamino) but-1-ynyl]phenyl}methyl)amino]-4-{4-[(4-chlorophenyl)phenylmethyl]piperazinyl}butanoate
48		CHIRAL R			621,2	4,97	methyl (2E)-3-[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]phenyl]prop-2-enoate
49		CHIRAL R			617,1	4,63	methyl (2E)-3-[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl]prop-2-enoate

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(71) Applicant *(for all designated States except US)*: UCB, S.A. [BE/BE]; Allée de la Recherche 60, B–1070 Brussels (BE).

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(75) Inventors/Applicants *(for US only)*: SCANNEL, Ralph [US/US]; 6 Cider Mill Road, Hopkinson, MA 01748 (US). CHATELAIN, Pierre [BE/BE]; 111 rue du Haras, B–1150 Woluwe Saint Pierre (BE). TOY–PALMER, Anna [US/US]; 20 Tanager Street, Arlington, MA 02476 (US). DIFFERDING, Edmond [LU/BE]; 55, route du Blocry, B–1348 Louvain–La–Neuve (BE). ELLIS, James [GB/US]; 287 Main Street, Boxford, MA 01921 (US). LASSOIE, Marie–Agnes [BE/BE]; 4, chemin du Bois de Clabecq, B–1440 Braine–Le–Chateau (BE). YOUNG, Michelle [US/US]; 827 Belmont Street, Belmont, MA 02478 (US). CAI, Xiong [CN/US]; 31 Oxford Avenue, Belmont, MA 02478 (US). HUSSOIN, Sajjat [US/US]; 61 Laconia Street, Lexington, MA 02420 (US). GREWAL, Gurmit [IN/US]; 2 Course Brook Lane, Natick, MA 01760 (US). LEWIS, Timothy [US/US]; 14 Temple St. Apartment 4E, Framingham, MA 01702 (US).

(74) Agent: LECHIEN, Monique; UCB, S.A. – Intellectual Property Department, Allée de la Recherche 60, B–1070 Brussels (BE).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: COMPOUNDS AND METHODS FOR TREATMENT OF ASTHMA, ALLERGY AND INFLAMMATORY DISORDERS

(57) Abstract

The present invention provides 1,4 substituted piperazines, 1,4 substituted piperidines, and 1–substituted,4–alkylidenyl piperidines compounds. The compounds of the invention are dual acting molecules having both leukotriene inhibition properties as well as antihistaminergic properties. The compounds of the invention are useful for treating conditions in which there is likely to be a histamine and/or leukotriene component. These conditions include preferably asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media. Also provided are methods of treating asthma and rhinitis by administering an effective asthma and rhinitis–relieving amount of the compounds to a subject in need thereof.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
16.76.WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/BE 00/ 00026	23/03/2000	26/03/1999
Applicant		
UCB, S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 00/00026

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/08 C07D295/12 C07D295/14 C07D307/[redacted] C07D307/52
A61K31/495 C07D401/04 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 616 596 A (BASHA ANWER ET AL) 1 April 1997 (1997-04-01) claims ---	1
A	US 4 525 358 A (BALTES EUGENE ET AL) 25 June 1985 (1985-06-25) cited in the application claims ---	1
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2000	02/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pauwels, G

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 00/00026

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 438 062 A (GANGULY ASHIT K ET AL) 1 August 1995 (1995-08-01) example 11 ---	23,24

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/126,521 26 March 1999 (26.03.1999) US

(71) Applicant *(for all designated States except US)*: **UCB, S.A.** [BE/BE]; Allée de la Recherche 60, B-1070 Brussels (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SCANNEL, Ralph** [US/US]; 6 Cider Mill Road, Hopkinson, MA 01748 (US). **CHATELAIN, Pierre** [BE/BE]; 111 rue du Haras, B-1150 Woluwe Saint Pierre (BE). **TOY-PALMER, Anna** [US/US]; 20 Tanager Street, Arlington, MA 02476 (US). **DIFFERDING, Edmond** [LU/BE]; 55, route du Blocry, B-1348 Louvain-La-Neuve (BE). **ELLIS, James** [GB/US]; 287 Main Street, Boxford, MA 01921 (US). **LASSOIE, Marie-Agnes** [BE/BE]; 4, chemin du Bois de Clabecq, B-1440 Braine-Le-Chateau (BE). **YOUNG, Michelle** [US/US]; 827 Belmont Street, Belmont, MA 02478 (US). **CAI, Xiong** [CN/US]; 31 Oxford Avenue, Belmont, MA 02478 (US). **HUSSOIN, Sajjat** [US/US]; 61 Laconia Street, Lexington, MA 02420 (US). **GREWAL, Gurmit** [IN/US]; 2 Course Brook Lane, Natick, MA 01760 (US). **LEWIS, Timothy** [US/US]; 14 Temple St. Apartment 4E, Framingham, MA 01702 (US).

(74) Agent: **LECHIEN, Monique**; UCB, S.A. - Intellectual Property Department, Allée de la Recherche 60, B-1070 Brussels (BE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW). Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

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8 February 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/58295 A3

(54) Title: COMPOUNDS AND METHODS FOR TREATMENT OF ASTHMA, ALLERGY AND INFLAMMATORY DISORDERS

(57) Abstract: The present invention provides 1,4 substituted piperazines, 1,4 substituted piperidines, and 1-substituted,4-alkylidenyl piperidines compounds. The compounds of the invention are dual acting molecules having both leukotriene inhibition properties as well as antihistaminergic properties. The compounds of the invention are useful for treating conditions in which there is likely to be a histamine and/or leukotriene component. These conditions include preferably asthma, seasonal and perennial allergic rhinitis, sinusitus, conjunctivitis, food allergy, scombroid poisoning, psoriasis, urticaria, pruritus, eczema, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, thrombotic disease and otitis media. Also provided are methods of treating asthma and rhinitis by administering an effective asthma and rhinitis-relieving amount of the compounds to a subject in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 00/00026

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/08 C07D295/12 C07D295/14 C07D307/14 C07D307/52
A61K31/495 C07D401/04 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5 616 596 A (BASHA ANWER ET AL) 1 April 1997 (1997-04-01) claims	1
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A	US 4 282 233 A (VILANI FRANK J) 4 August 1981 (1981-08-04) cited in the application claims	1
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-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2000	02/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pauwels, G

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INTERNATIONAL SEARCH REPORT

Intr[redacted]Application No
PCT/BE 00/00026

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 438 062 A (GANGULY ASHIT K ET AL) 1 August 1995 (1995-08-01) example 11	23,24

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int Application No
PCT/BE 00/00026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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